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**Studies
on
Azotemic
Renal
Osteodystrophy**

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STUDIES ON AZOTEMIC RENAL OSTEODYSTROPHY

by

Birger Lindergård



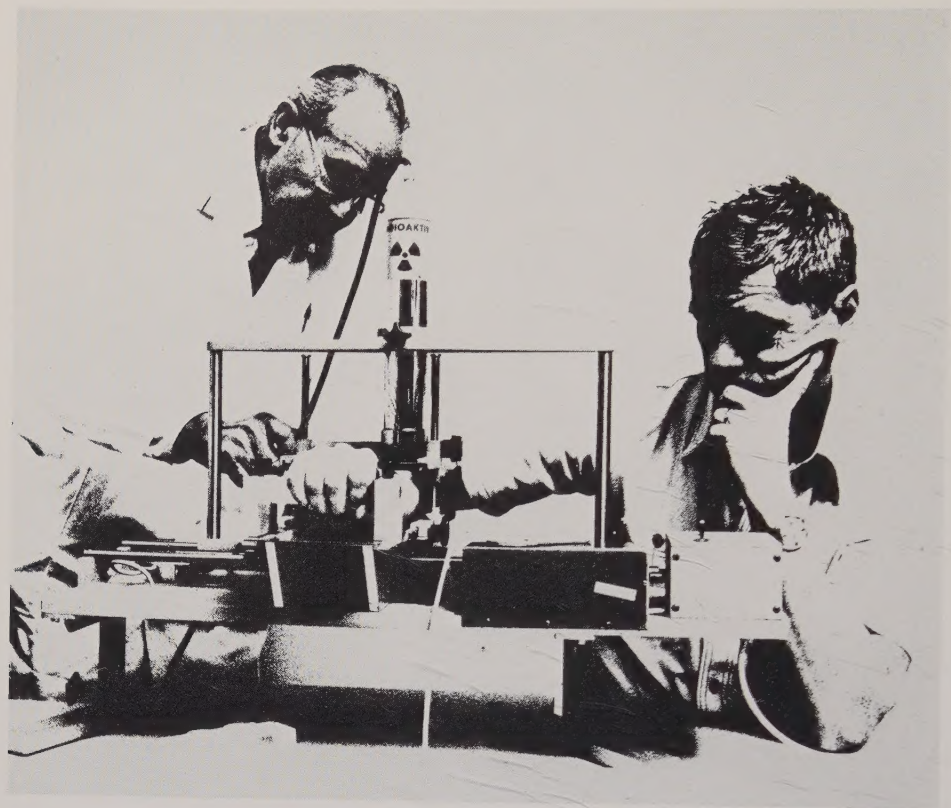
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To my wife and
our daughters.



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This thesis is based on the following papers:

- I Lindergård, B. 1981. Bone mineral content measured with photon absorptiometry - a methodological study carried out on normal individuals. Accepted for publication in Scand J Urol Nephrol.
- II Lindergård, B. Changes in bone mineral content evaluated by photon absorptiometry before the start of active uremia treatment. Accepted for publication in Clin Nephrol.
- III Lindergård, B., Gullstrand, P., Rydmarker, S. & Tibblin, S. 1977. Clinical evaluation of bone-densitometry in patients with final renal insufficiency operated for hyperparathyroidism. Scand J Urol Nephrol 11, 59 - 67.
- IV Johnell, O., Lindergård, B., Nilsson, B.E. & Wiklund, P.E. Bone morphologic parameters of renal osteodystrophy in patients on regular hemodialysis. Submitted for publication in Nephron.
- V Lindergård, B., Lindholm, T., Sandström, S. & Johnell, O. 1981. Renal osteodystrophy in patients dialyzed for 10 years or more. Accepted for publication in Kidney Int.

These articles will be referred to by their Roman numerals in the text.

Abbreviations used in the text:

RDT	regular hemodialysis treatment
PTH	parathyroid hormone
BMC	bone mineral content
BMC/W	bone mineral content divided by bone width
GFR	glomerular filtration rate
HPT	hyperparathyroidism

INTRODUCTION

Osteodystrophy is a word derived from the Greek signifying poorly nourished bone. The term "renal osteodystrophy" was introduced by Liu and Chu in 1943 for the skeletal complications connected with renal disease. Stanbury later (1957) changed the term to "azotaemic renal osteodystrophy" to imply that the skeletal changes were secondary to renal disease with azotemia.

The first cases of bone disease related to renal disease were probably described by Clement Lucas in 1883 as "Form of late rickets associated with albuminuria, rickets of adolescents".

Since the work of Albright in 1937 more attention has been paid to the bone disease osteitis fibrosa and to such an extent that "late rickets" was discussed as a cause of azotemic renal osteodystrophy.

In the early 1960's regular hemodialysis treatment (RDT) of patients with chronic uremia became possible (Scribner 1960, Alwall et al. 1963, and others). It soon became apparent that bone disease in these patients was a major problem (Pendras & Erickson 1966, Johnson et al. 1967, Thomson et al. 1967, Weller et al. 1968, Katz et al. 1969, Kleeman et al. 1969, Stanbury et al. 1969).

The azotemic renal osteodystrophy now came to involve the entire spectrum of the different bone diseases seen, mostly roentgenologically, such as bone loss or osteoporosis, rickets or osteomalacia, osteosclerosis, osteitis fibrosa, and extraskeletal changes such as soft tissue and vessel calcification. Usually several abnormalities were seen in the same patient.

The mechanism leading to the renal osteodystrophy is complex. A simplified diagram is given in Fig. 1.

With the progress of renal insufficiency several substances are retained such as phosphate, parathyroid hormone (PTH) metabolites, hydrogen ions, vitamin A, calcitonin and pyrophosphate.

The decreased renal mass and the phosphate retention are held responsible for the defective synthesis of the active vitamin D metabolite, $1,25(\text{OH})_2\text{D}_3$ (Massry 1980). In the pure form of vitamin D deficiency the calcium absorption in the gut is lowered, the S-calcium will fall and because of the lack of calcium, the bone will be poorly mineralized leading to rickets in children and osteomalacia in adults.

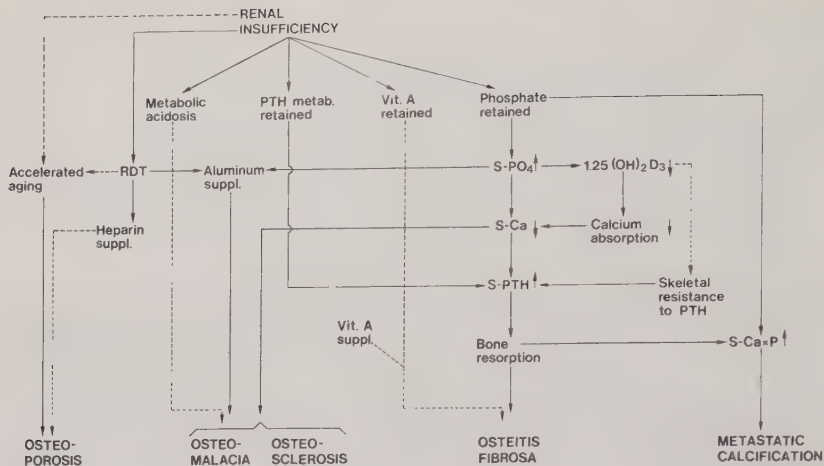


Figure 1. Diagram over mechanisms leading to renal osteodystrophy. Solid lines indicate confirmed mechanisms and broken lines tentative mechanisms.

Metabolic acidosis may also contribute to the pathogenesis of osteomalacia, either by a direct bone dissolving effect (Epstein 1968) or by inhibiting bone alkaline phosphatase (Cochran & Wilkinson 1975). Others have disputed the role of acidosis as a cause of bone disease (Stanbury 1972) or considered it of minor importance (David 1977).

When there is an abundance of bone mass, although poorly mineralized, the bone becomes less radiolucent and visualized as osteosclerosis (David 1977).

As a consequence of the lowered S-calcium the parathyroid glands are stimulated to increased production of PTH. The phosphate excretion will then increase, the calcium excretion decrease, the calcium dissolution of the skeleton increase and the synthesis of $1,25(\text{OH})_2\text{D}_3$ be stimulated. Moreover as there is a resistance to the effect of PTH on the bone, possibly due to the defective $1,25(\text{OH})_2\text{D}_3$ synthesis, a further increase in serum level of the PTH will be the result (Massry et al. 1973, Coburn 1980, Massry et al. 1980).

In uremia the S-PTH is closely related to the S-creatinine (Fuss et al. 1976, Christensen & Nielsen 1977) but in certain patients the S-PTH is extraordinarily elevated leading to increased osteoclastic resorption, marrow fibrosis and to osteitis fibrosa.

When the S-calcium phosphate product is elevated above 4.9 (mmol/l) there

is a risk of metastatic calcification either as amorphous calcium phosphate in viscera and skeletal muscles or as apatite crystals in vessel walls or joints (Kuzela et al. 1977, Velentzas & Oreopoulos 1979).

Calcitonin is considered to prevent the bone from the dissolving effect of PTH. The S-calcitonin is increased in most uremic patients due to a decreased degradation and/or excretion (Silva et al. 1977, Nielsen et al. 1979).

The role of calcitonin has been elucidated in patients who were bilaterally nephrectomized (Heynen et al. 1976, Kanis et al. 1977). After nephrectomy the S-calcitonin increased in parallel with a decrease in bone turnover.

Furthermore calcitonin has been given with beneficial results to patients on RDT (Quarto di Palo 1977, Feletti & Bonomini 1979).

The pyrophosphates are reported to be elevated in uremic patients both in serum and bone (Russell et al. 1969, Alfrey et al. 1976).

The role of pyrophosphate may be to delay the mineralization of bone and to enhance extraosseous calcification (Alfrey et al. 1976) which effect could be reversed by diphosphonate (Zucchelli et al. 1978).

Bone loss or osteoporosis may be caused by an accelerated aging process in uremia, heparin (see below), immobilization (Bishop et al. 1972), inadequate protein- and calorie-intake (Malluche et al. 1976) or secondary hyperparathyroidism (HPT).

Additional mechanisms:

To these mechanisms in the development of renal osteodystrophy should be added those superimposed by the treatment of the end-stage renal failure.

Aluminum has been found to cause not only the tragic form of brain damage known as dialysis encephalopathy but also osteomalacic osteodystrophy (Parkinson et al. 1979, Drüeke 1980). The most important source of aluminum is the dialysis fluid (Platts et al. 1977, Elliot et al. 1978). Another source may be the aluminum-containing phosphate binders (Marsden et al. 1979).

Vitamin A, which is retained in uremia, may have a function on bone similar to PTH (Yatzidis et al. 1975, Werb et al. 1979), and heparin has been claimed to cause osteoporosis (Griffith et al. 1965, Henderson et al. 1979) or a defect similar to that seen in hyperparathyroidism (Schuster et al. 1969). The dialysis fluid may also contain fluoride which may cause osteomalacia (Posen et al. 1972, Cordy et al. 1974) an effect which is questioned

by others (Rao & Friedman 1975).

Furthermore, the dialysis fluid must contain a sufficient amount of calcium to avoid the risk of stimulation of the parathyroid glands (Goldsmith et al. 1975). On the other hand, with too elevated calcium concentration there is a risk of acute or chronic calcium intoxication (e.g. Rivera-Vazquez et al. 1980). Also the magnesium content in dialysis fluid is of importance as a low S-Mg may cause a skeletal resistance to PTH (Mennes et al. 1978, Freitag et al. 1979) and a high S-Mg may interfere with the mineralization of bone (Alfrey & Miller 1973).

Finally anticonvulsant drugs such as phenytoin and phenobarbital may induce the hepatic microsomal enzymes to increased catabolism of $25(\text{OH})\text{D}_3$ leading to osteomalacia (Jubitz et al. 1977, Hahn & Avioli 1975), and possibly uremia per se may act enzyme-inducing (Maddocks et al. 1975).

Methods for studying renal osteodystrophy.

It is our opinion that the full arsenal of available diagnostic procedures should be used in order to evaluate different aspects of the renal osteodystrophy.

S-calcium, S-phosphate, S-alkaline phosphatase.

Total serum calcium can be divided into a protein-bound (40 %) and a diffusible fraction (60 %). This fraction can be further separated into complex-bound (4 % of total calcium) and free calcium ions (56 %) (Massry et al. 1977). In the uremic state the complex form of calcium is elevated to an unpredictable degree, so ionized calcium should be measured and not calculated from S-albumin (Conceicao et al. 1978). In the present study it was, however, possible to measure only the total calcium.

S-phosphate should be measured simultaneously with S-calcium in order to calculate the calcium phosphate product. This product is of great importance for predicting the risk of metastatic calcifications. S-alkaline phosphatase is regarded as a parameter of osteoblastic activity (Nordin 1973). Probably the alkaline phosphatase plays an important role in the primary calcification of cartilage by possessing pyrophosphatase activity (Fleisch & Russell 1977). Bone iso-enzymes have lately been suggested as a better parameter to follow than total alkaline phosphatase (Siede et al. 1980).

S-parathyroid hormone (PTH).

This 84 amino acid hormone is metabolized in the liver and kidney to both carboxy- and amino-terminal PTH fragments. The C-terminal fragments are

further metabolized in the kidney, while the N-terminal fragments mediate the effect of PTH on bone (Martin et al. 1980).

Different laboratories measure different fragments depending on available immune serum. Although the N-terminal fragment seems to be the metabolic active form, the C-terminal fraction is more closely correlated to the clinical findings (Coburn 1980). The antiserum (Burroughs and Wellcome) used in this study is directed mainly towards the C-terminal PTH and has been found to correlate well with the clinical observations.

Diagnostic radiology.

The radiographic techniques used to study renal osteodystrophy can be divided into conventional radiography (macro-radioscopy) and radiography with magnified viewing (micro-radioscopy). To answer the question where on the skeleton radiographic examinations should be performed to obtain the most information a study was made of 78 dialysis patients. Hands, feet, lower legs, spine, pelvis and shoulders were examined simultaneously (Lindergård & Sandström, unpublished observations). The various findings of decalcification, subperiosteal resorption, soft tissue and vessel calcification and sclerosis were graded after a point scale (Fig. 2). It was found that examination of the hands was the most rewarding.

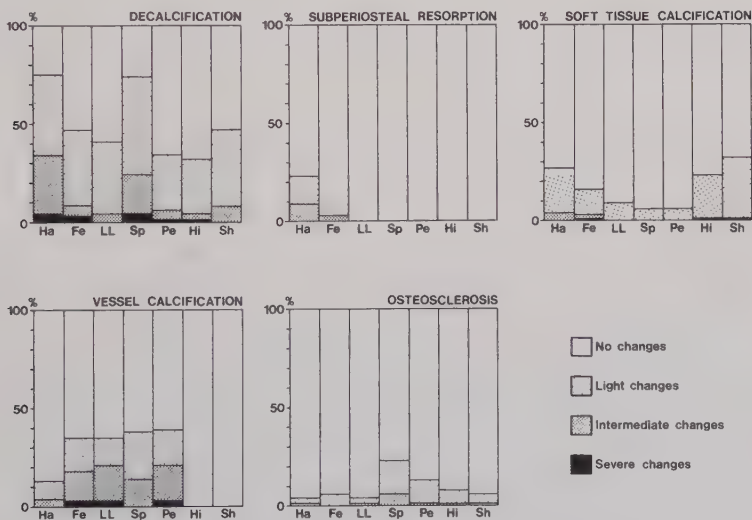


Figure 2. Radiological findings in 78 patients on RDT who underwent simultaneous examinations of hands (Ha), shoulders (Sh), spine (Sp), pelvis (Pe), lower legs (LL) and feet (Fe).

By micro-radioscopy (Meema et al. 1972) it is possible to differentiate between periosteal, intracortical and endosteal resorption and thus cortical bone can be studied which is difficult to do histologically. Morphometric studies mainly on the 2nd metacarpal bone (Barnett & Nordin 1960, Exton-Smith et al. 1969 and others) give information of bone mass as a parameter of osteoporosis.

Bone histology.

Bone histologic analysis is often performed on trabecular bone from the iliac crest using the Burkhardt instrument (Burkhardt 1966). The sample is studied undecalcified. Cortical bone is rarely studied because the bone specimen, usually a part of a rib, has to be removed surgically.

Several histo-morphometric parameters can be used for evaluation of the degree of mineralization in relation to bone mass. Evaluation of the number of osteoclasts can be used as a parameter of hyperparathyroidism. Tetracycline double labeling is used to study the mineralization per unit of time. Furthermore, the dynamic aspects of bone remodelling can be studied by identification of pertinent cells and by use of bone seeking isotopes. Bone mass may be estimated but often with a large scatter.

In the present study the degree of mineralization was expressed as the osteoid surface in per cent of trabecular bone surface (Wiklund 1980) and parathyroid activity as the osteoclast count (Johnell 1980). The variation coefficient for measuring the amount of osteoid is as high as 20 %, but because the deviation from normal is often pronounced in uremic patients the method is still useful. The precision of the osteoclast count is also acceptable.

Photon absorptiometry (I).

As photon absorptiometry is one of the main techniques used in this study of renal osteodystrophy it will be discussed in more detail.

Photon absorption techniques measure the amount of mineral, mainly calcium, in a cross-section of a part of the skeleton. The width of the individual bones can be calculated from the speed of a scanner. It is not possible to measure the cortical bone separately and hence there is no direct information about bone mass. The bone mineral content (BMC) is often used as a parameter of bone mass as there is a relationship between BMC and bone mass in healthy individuals. If, however, the relationship is disturbed as especially in osteomalacia, the BMC can not be regarded as a parameter of bone mass.

The technique used in this study is principally the same as the one first described for clinical use by Cameron and Sorenson in 1963 (Cameron & Sorenson 1963). A new instrument was presented by Naucière et al. in 1974 and was then slightly modified by us (Lindergård et al. 1974). This instrument is now commercially available as Gambro^(R) Bone Mineral Detector, AB Gambro, Lund, Sweden. The measuring procedure is presented in (I). In order to improve the reproducibility, which was mainly impaired by problems in repositioning the arm, we introduced the following procedure (Lindergård et al. 1974). A device was constructed for measuring the length of the forearm from the tip of the olecranon to the styloid process of ulna. This distance was then transferred to a built-in scaler in the scanner. The arm was fastened in a special holder in the scanner in an elevated position which kept the bones of the arm well separated and the tip of the olecranon pressed against a metal stopper. In this way the measuring point could be fixed accurately without the need of penmarkings on a movable skin. Measurements were routinely done at a distance of 75 % of the length of the arm down from the tip of the olecranon. A print-out of the photon absorption data was scrutinized for errors in the baseline setting. By these means the reproducibility was 0.3 - 1.0 % in a phantom and 1.6 - 2.1 % in patients (Lindergård et al. 1974).

The coefficient of variation when measuring the same arm repeatedly without repositioning was 1.5 % as compared to 2.5 % with repositioning. The long time stability when measuring on a phantom is good (Lindergård 1977, and updated in Fig. 3).

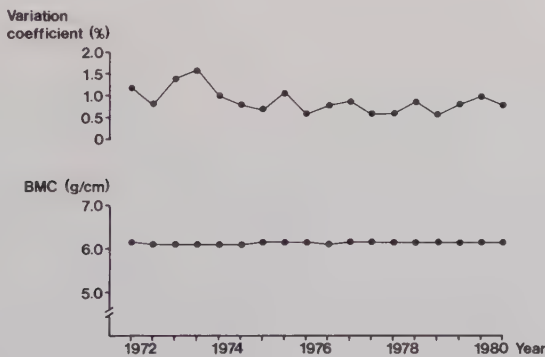


Figure 3. Mean and coefficient of variation of "BMC" in a phantom measured 10 times at the beginning of each year since 1972.

The accuracy of the photon absorption technique has been studied by measuring on a part of bone which has then been either weighed directly or first burnt to ash and then weighed, or the calcium content measured spectrophotometrically. The correlation coefficients were 0.86 - 0.99 (Cameron et al. 1968, Mazess 1971, West 1973, Karjalainen 1973, Christiansen et al. 1975). The accuracy of the photon absorption technique has also been studied by comparing with the results obtained from measuring with the whole body neutron activation technique. This comparison gave correlation coefficients of 0.86 - 0.94 (West 1973, Cohn et al. 1975, Manzke et al. 1975).

The crucial question is whether the bone mineral content of the measured part of the skeleton is representative for the whole skeleton. The fairly good correlations to the results obtained by whole body neutron activation support this concept. It has also been shown that there are correlation coefficients of 0.87 - 0.90 when comparing the BMC in, for example, a forearm with that of the whole skeleton either by weighing the different parts or by measuring the calcium content in ash from bone (Mazess 1971, Christiansen et al. 1975). On the other hand poor correlations have been found between the BMC in appendicular skeleton, for example the forearm bones, and the axial skeleton, the spine (Dalén & Jacobson 1974) whereas the intercorrelations between different parts of the appendicular skeleton were generally good (Mazess 1971, Dalén & Jacobson 1974, Manzke et al. 1975).

The bone in the midshafts of the forearm is mainly cortical whereas it is more trabecular in the distal part (Schlenker 1976). Also in uremic patients there was a good correlation, $r = 0.91$, between the BMC in the midshafts and the distal parts of the forearms when measuring with our photon absorption technique (Lindergård 1977). We could also show that the BMC in one arm correlated strongly to that of the other one in normal individuals, $r = 0.97$ (I). The poor correlation between the BMC in the appendicular and the axial skeleton is a drawback to the technique. On the other hand a "highly reproducible measurement on the limbs may in fact provide more information even on the axial skeleton than an imprecise determination on the spine itself" (Mazess 1971). Furthermore, it is not necessarily so that the BMC in the spine is the most representative parameter of bone disease, not even in osteoporosis (Johnston et al. 1968).

The results when measuring on 45 patients on regular hemodialysis treatment (RDT) were compared with the results of measurements with another commercially available instrument (Bone Scanner 7100, Studsvik, AB Atom-

energi, Nyköping, Sweden). The results were closely correlated, $r = 0.97$ (Lindergård et al. 1974).

The influence of fat content in the arm was found to be a source of error which has to be taken into consideration (Lindergård & Naversten 1978). This is important when comparing with normal individuals as was exemplified in a study on lithium-treated patients who were found to be more obese than our reference group (Thysell et al. 1981). It is also of importance when following patients who change significantly in the amount of fatty tissue. The measured BMC may be corrected for fatty tissue as suggested (I, II) but still there is no ideal solution to this problem. Some instruments (e.g. Norland-Cameron, Norland Instruments, Wisconsin, USA) use the photon absorption in the soft tissue between the bones of the forearm as a reference level instead of the absorption in water as in our method. However, one has to take into consideration the possibility of calcifications in this area. Although the soft tissue absorption was found to be mainly a parameter of fat tissue (I), the correlation to the other fat parameters decreased in strength in the older age groups. The explanation could be that there is an increase of soft tissue calcification with age parallel to a decrease in BMC (I).

In uremics it is known that there is an increase in soft tissue calcification (Kuzela et al. 1977) and if the calcium is deposited also between the bones of the forearm a false low value of BMC would be the result when using the soft tissue as a reference level.

Normative data (I).

As a reference group we used 136 adults and 14 children on whom measurements were performed on both arms. The BMC correlated positively with weight, height, body surface and length of the forearm. The often used unit BMC/W introduced by Johnston et al. in 1968 (BMC divided by bone width (W)) was also found to correlate with the various body parameters. Thus, some kind of standardization to the body size would be suitable. As, however, there were great differences between the sexes in BMC/W and some body parameters, no common denominator could be found. This was also the experience of Dequeker et al. (1978) who introduced the concept of iso-width curve where the BMC was correlated to age for varying widths of the radius. Others have normalized to height and arm span in a best-fit power curve (Harrison et al. 1978) or perhaps better to the lean body mass (Cohn et al. 1978).

Our sample of normal individuals was taken mostly from hospital personnel.

The sample has recently been enlarged with a selection from the general population (Fig. 4). Probably due to larger body size the BMC/W was slightly higher in some age groups of this additional sample.

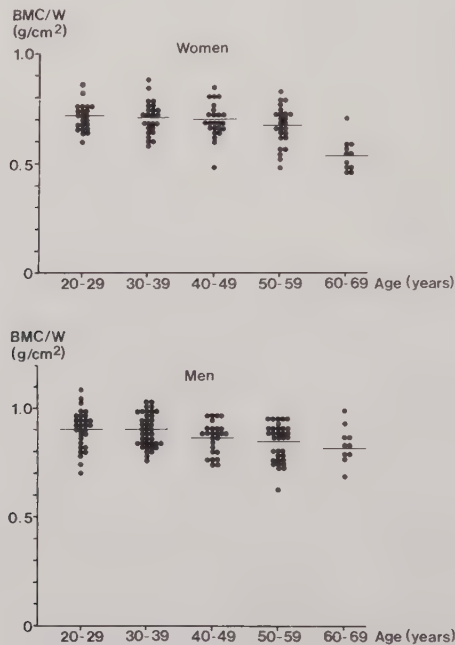


Figure 4. BMC/W in an enlarged sample of normal individuals.

Azotemic renal osteodystrophy before the start of active uremia treatment (II).

There are few reports on the natural history of renal osteodystrophy before the start of active uremia treatment. Nichols et al. (1972) in a histologic study noted that virtually all patients with end-stage renal failure had signs of bone disease. Peart & Peart (1973) studied 60 patients with a blood urea above 100 mg% and noted that osteitis fibrosa was the most prominent histologic feature occurring in 93 % of the patients and that osteomalacia develops subsequently. Malluche et al. (1976) studied the bone histology in incipient and advanced renal failure. Signs of secondary hyperparathyroidism were found already at a GFR below 50 ml/min. and a mineralization defect was seen in many patients at a GFR below 40 ml/min.

In a roentgenological study Tatler et al. (1973) extrapolated the development of bone disease during active uremia treatment to the time before the start and concluded that erosions appeared at 2.4 years, peri-articular calcification at 1.5 years and vascular calcification at 1.0 year before the start of RDT.

Studies of the BMC with photon absorption technique before active uremia treatment are few (II).

We studied the BMC longitudinally in 74 patients followed up to 24 months before the start of active uremia treatment. In 64 of the 74 patients there was a decrease in BMC. The starting point of this decrease could for the whole group be calculated to 21 months before the start of active uremia treatment which is in agreement with the results of Tatler et al. (1973). The decrease was particularly fast in patients not given extra calcium and/or vitamin D. As a result of this decrease the BMC was low at the start of active uremia treatment. During the first year of RDT the decrease was turned into a slight increase in BMC. These results point to the importance of treating the bone disease early in the progress of uremia. The finding that the supplementation of calcium and/or vitamin D might reduce the speed of mineral loss gives a hint of suitable treatment which can be very efficient (Healy et al. 1980). On the other hand there may be a risk in giving potent vitamin D preparations as the uremic kidney may be vulnerable to calcium and phosphate overload (Weisbrode & Capen 1977, Christiansen et al. 1978, Bell & Stern 1978, Benabe & Martinez-Maldonado 1978, Haut et al. 1980, Massry et al. 1980, Yoshiyama et al. 1980).

Phosphate restriction seems promising in preventing not only the secondary hyperparathyroidism and the resulting bone disease but also a further deterioration in kidney function (Slatopolsky et al. 1972, Bricker 1972, Ibels et al. 1978, Kaplan et al. 1979). The phosphate restriction can probably be included in a protein reduced diet (Walser et al. 1979, Giordano 1980).

In our study it was noticed that patients on protein reduced diet did not differ from patients on an ordinary diet in the speed of mineral loss before active uremia treatment. However, most of our patients were supplemented with calcium and/or vitamin D. Some of the few who were not supplemented lost mineral very fast, up to 2.8 % per month for 11 months.

Secondary hyperparathyroidism, HPT (III, V).

Laboratory signs of secondary HPT are seen in most uremic patients (Fuss et al. 1976, Christensen et al. 1977). The skeletal complication of secondary HPT, osteitis fibrosa, can often be seen already at the start of active uremia treatment (Tatler et al. 1973). This was also the case in a group of patients followed for more than 10 years on RDT (V). In this group, osteitis fibrosa was the most dominant bone disease. This may reflect an early era of the RDT when patients were less well dialyzed, the calcium content in the dialysis fluid was too low, the phosphate control was poor and the secondary HPT was not treated surgically or with vitamin D analogues. Parathyroidectomy, if performed early in the dialysis course, was found to be beneficial according to laboratory and radiographic investigations. The BMC, as evaluated by photon absorption technique, also improved in some patients. If the parathyroidectomy was performed late, however, there was little change.

In a group of RDT-patients followed with photon absorptiometry before and after parathyroidectomy the BMC was significantly lower at the time of operation in comparison with normals and other RDT-patients (III). Before parathyroidectomy there was no significant change, but after operation the BMC increased in half of the patients and significantly in the whole group of patients.

A sharp decline in BMC was observed in four of ten patients within the first months after the parathyroidectomy. Thereafter there was a steady increase. Such a dramatic decline in BMC, in one patient 25 %, is scarcely described in the literature (Hosking et al. 1972, Dalén & Hjern 1974). The mechanism is unclear, but since the parathyroidectomy was total the sudden drop in PTH might have lowered the synthesis of $1,25(\text{OH})_2\text{D}_3$ and thus the S-calcium. Obviously the low S-calcium often seen, could not be explained by calcium moving into the skeleton, at least not into the midshafts of the forearms.

After parathyroidectomy most patients could be supplemented with calcium and vitamin D metabolites, which was not possible before the operation. This is in accordance with the assumed resistance to vitamin D seen in certain patients and may be a cause of treatment failure (Massry et al. 1980, Healy et al. 1980). Massry and coworkers have maintained that PTH is the uremic toxin "X". (Massry 1977, Massry & Goldstein 1978, Massry & Goldstein 1979, Massry 1979), and other groups have confirmed its damage on various organ systems (Gatewood et al. 1975, Zingraff et al. 1978,

Avram et al. 1978, Avram et al. 1979, Barbour 1979, Drüeke et al. 1980).

There was no significant increase in hemoglobin in our patients but either the group is too small or the operation performed too late with already established myelofibrosis. The damage on peripheral nerve conduction, central nervous function, sexual function, lipid metabolism or left ventricular function was not studied.

The medical treatment of HPT with propranolol (Drüeke et al. 1975, Caro et al. 1978) or cimetidine (Jacob et al. 1980, Sherwood et al. 1980) needs further confirmation.

Bone histology in azotemic renal osteodystrophy (IV).

In 72 patients on RDT for 1 - 95 months, bone biopsy was taken from the iliac crest and the trabecular bone was studied undecalcified for: trabecular volume as a parameter of bone loss, osteoid surface as a parameter of osteomalacia and osteoclast count as a parameter of osteitis fibrosa.

According to the morphologic criteria used in this study 20 patients had no bone disease, 3 had osteomalacia alone, 27 had osteitis fibrosa and 22 had a combined bone disease. That 28 % of the patients were judged to have no bone disease is in contrast with the results of Nichols et al. (1972) where some kind of bone disease was present in virtually all patients. However, it is well known that the severity of bone disease varies greatly from centre to centre (Kerr 1973).

Pure osteomalacia was found in only 4 % which is in accordance with others (Duursma et al. 1974, Alvarez-Ude et al. 1978). Osteomalacia, however, is often combined with osteitis fibrosa.

The osteoclast count correlated to S-PTH, S-alkaline phosphatase, $S-PO_4$ and to duration in hemodialysis. Others have observed a good correlation between bone disease, in particular osteitis fibrosa, and S-alkaline phosphatase (Duursma et al. 1974, Alvarez-Ude et al. 1978) and especially the bone isoenzyme of alkaline phosphatase showed high correlation to bone disease (Pierides et al. 1979, Siede et al. 1980).

An osteoclast count higher than in other patients was noted in those patients who later were parathyroidectomized. The biopsy technique can thus be used in the diagnosis of severe secondary HPT. Those patients who had been bilaterally nephrectomized did not deviate from other patients in occurrence of osteoid surface or osteoclast count which is in agreement with the results of Bordier et al. (1973). In fact favourable effects of

nephrectomy have been reported (Kanis et al. 1977) which have been ascribed to the increase in S-calcitonin.

Patients with polycystic kidney disease and interstitial nephritis were found to have more severe osteomalacia than patients with glomerulonephritis. This difference may be due to the longer duration of uremia often seen in the patients with polycystic kidneys or interstitial nephritis and/or a more severe defect in the synthesis of active vitamin D metabolites. Similarly the BMC at the start of active uremia treatment were lower in these patients (II).

Long term follow-up of RDT-patients (V).

According to the latest available EDTA statistics (Brunner et al. 1979) about 350 patients from European centres have been treated for at least 10 years with hemodialysis, RDT.

Among our RDT-patients, two have been on uninterrupted RDT for more than 16 years, which is probably the longest duration in Europe (Gurland et al. 1976). These two patients and eight others, who have been on RDT for more than 10 years, were followed with diagnostic radiography from the start, bone densitometry since 1972 and bone histology since 1971. There was a steady increase in most of the radiological findings such as decalcification, resorption and calcification. The subperiosteal and unguis tuft resorption representing osteitis fibrosa was the most prominent problem. Metastatic calcification in small vessels and soft tissue was noted in most patients and often deteriorated after supplementation with $1-\alpha\text{D}_3$.

As a parameter of bone volume the cortical thickness index (Barnett & Nordin 1960) was measured. This index decreased steadily in eight of 10 patients showing significant straight lines with a slope of from 0.03 to 0.13 % per month or 3.6 to 15.6 % per 10 years. This bone loss was exceptionally fast as only one was a postmenopausal woman, who actually lost only 0.03 % per month. This index has not been widely used in RDT-patients (Bone et al. 1972, Ritz et al. 1973, Del Rio 1978, Meema et al. 1978, Henderson et al. 1979).

The cause of the bone loss is often assumed to be secondary HPT (Ritz et al. 1973, Bone et al. 1972), which is in accordance with our experience that the cortical thickness index increased in some patients after parathyroidectomy. However, our two patients who lost bone mass fastest were the only two who never had signs of secondary HPT. This cause of bone loss has also been disputed by e.g. Henderson et al. (1979) who found a correlation with heparin consumption. Other mechanisms that may be in-

volved in the developing of bone loss are immobilization (Bishop et al. 1972, Malluche et al. 1976), inadequate protein- and calorie-intake (Malluche et al. 1976) or just an accelerated aging. The BMC was low or very low in most patients but showed little change during the eight years they were followed. In two patients an improvement was noted after early parathyroidectomy.

In two of the patients followed for the largest number of years an unusual blunted profile was noticed in the photon absorption curve. The cause of this profile is probably a severe intracortical mineral loss, opposed to that seen in elderly people who mainly have an endosteal mineral loss presenting as a deep excavation in the photon absorption profile (Lindergård & Naversten 1978).

CONCLUSIONS:

The azotemic renal osteodystrophy was followed with laboratory, roentgenographic, histologic and/or photon absorptiometric investigations before active uremia treatment, during RDT, on RDT before and after parathyroidectomy and on RDT for more than 10 years. The following conclusions can be drawn:

1. Photon absorptiometry is a simple, accurate and reliable technique both for screening and for following the BMC in patients on RDT.
2. Certain drawbacks of this technique must be considered such as the influence of fat tissue and the size of the skeleton.
3. Patients on RDT have low BMC mainly because they lose mineral before the start of active uremia treatment.
4. The BMC was low in patients who developed signs of secondary HPT and increased after successful operation.
5. In some patients there was a transient decrease in BMC after parathyroidectomy.
6. Bone biopsy is a valuable tool for the investigation of the degree of osteomalacia and for early diagnosis of osteitis fibrosa.
7. S-alkaline phosphatase and S-PTH were the laboratory tests with the best correlation to the bone disease.
8. In patients on long term RDT, most showed a steady increase in the roentgenological findings.
9. The progress has been halted, only after parathyroidectomy and treatment with modern vitamin D analogues.

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To all the patients I am deeply indebted for their patience.

"This is very strange", said Mr. Pickwick (fell) upon his knees
before the little stone. (Dickens 1836).

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BONE MINERAL CONTENT MEASURED WITH PHOTON ABSORPTIOMETRY
- A METHODOLOGICAL STUDY CARRIED OUT ON NORMAL INDIVIDUALS

by

Birger Lindergård

ABSTRACT

Bone mineral content (BMC) was measured by photon absorptiometry in 136 adults and 14 children in order to obtain a reference group. The radiation source was ^{241}Am (45 mCi) and measurements were made on the midshafts of both forearms. The baseline level for measurements was the photon absorption through a waterfilled rubber cuff applied around the arm.

Positive correlations were found between BMC and body parameters such as weight, body surface area, height, arm length and bone width. Negative correlations were found between BMC and fat parameters such as the size of a hump adjacent to the bone in the photon absorption profile, skin fold thickness, body mass index and the photon absorption between the bones. Therefore the measured BMC should be corrected for one of the fat parameters and probably also for a body parameter.

As a means to correct for fat tissues a baseline level for photon absorption through soft tissue between the bones was compared to the use of a baseline level through water. BMC seemed to be higher in the dominant than in the non-dominant arm. However, after correction for fatty tissue there was no significant difference. BMC seemed to increase with intake of milk products. No correlation could be shown to physical exercise, pregnancies, duration of lactation, or smoking.

Skeletal changes have proved to be an important problem in patients with advanced renal failure as well as in patients on regular hemodialysis or patients with kidney transplants (e.g. David, 1977).

There are now a number of different methods for diagnosing and following the skeletal changes. By means of diagnostic radiology, various types of skeletal changes have been shown (Cohen, Cohen, Ahad & Kaye, 1970; Tatler, Baillod, Varghese, Young, Farrow, Wills & Moorhead, 1973; Ritz, Krempien, Mehls & Malluche, 1973; Moorhead, Tatler, Baillod, Varghese, Wills & Farrow, 1974; Parfitt, 1977). Evaluation of the bone structure can also be made (Meema, Rabinovich, Meema, Lloyd & Oreopoulos, 1972; Calenoff & Norfray, 1973; Eastwood, Bordier & de Wardener, 1973). Furthermore, morphometric measurements have been developed for assessment of the quantity of bone mass (Barnett & Nordin, 1960; Meema et al., 1973).

All the roentgenological methods have in common that they are readily available, convenient for the patient and can thus be repeated as often as needed. They are also a necessary complement to other methods in surveying the extent of skeletal damage. The disadvantage of the roentgenological methods is that the amount of mineral content is difficult to evaluate. If more detailed information is required much time- and skill-consuming work is needed.

Bone biopsy is often carried out at the larger dialysis centres. A good assessment can be made of the degree of mineralization, the quantity of bone mass and, according to some investigators, the degree of changes due to hyperparathyroidism (Eastwood et al., 1973; Ritz et al., 1973; Malluche, Ritz, Lange, Kutschera, Hodgson, Seiffert & Schoeppe, 1976; Ritz, Malluche, Krempien & Mehls, 1977). One of the disadvantages of bone biopsy is that only a very small sample of the skeleton is examined. Furthermore, the procedure is not very popular among the patients and therefore cannot be repeated as often as needed.

The photon absorption technique for assessment of BMC was first described for clinical use by Cameron and Sorenson in 1963. This technique has later on been modified in several ways. (E.g. Nauclér, Nilsson & Westlin, 1974; Lindergård, Lindholm & Naversten, 1974). Photon absorptiometry has many advantages over other methods. Our method (Lindergård, et al. 1974) ^{x)} is quick and easily handled and convenient for the patient. A large number of measurements can therefore be made on the same patient over shorter or longer periods. The method is considered reliable (Cameron, Mazess & Sorenson, 1968; Mazess, 1971; Manzke, Chesnut, Wergedal, Baylink & Nelg, 1975) and the reproducibility is good (Lindergård et al., 1974).

The aim of this study was to obtain our own sample of controls and to find out how different body parameters influence the result.

MATERIAL

The normal sample comprised 154 individuals: 136 adults of whom 59 were women and 77 men, aged 20 to 69 years and 14 children, all 12-year-old. The age and sex distribution is shown in fig. 1.

The majority of the adults were working in our hospital, representing different employment categories with varying degrees of physical activity. Only perfectly healthy individuals without a history of skeletal damage were included.

^{x)} Gambro Bone Mineral Detector

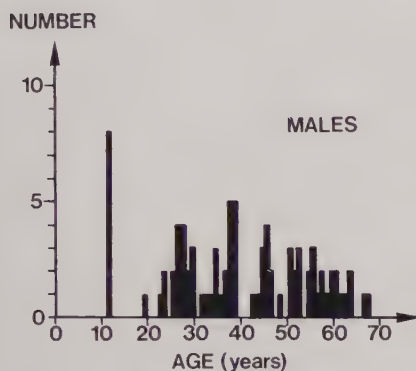
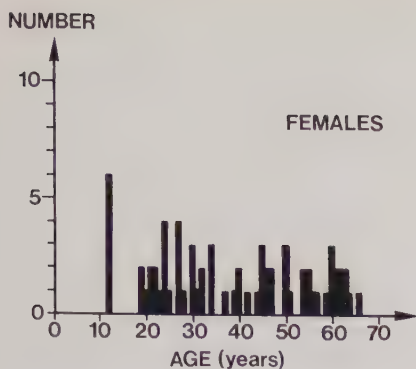


Figure 1. Sex, age and number of subjects in the normal material.

METHODS

The mineral content in both arms was measured by photon absorptiometry. As a radiation source we used ^{241}Am with an activity of about 45 mCi and a photon energy of 60 keV. The radiation source and the detector were built as one unit for scanning a cross-section of the forearm. The site of this cross-section was the border between the distal and 2nd distal quarter of the distance between the tip of the olecranon and the tip of the processus styloides ulnae. The scanning speed was 10 mm/min. A waterfilled rubber cuff was carefully applied around the arm at the site of the measurement. The cuff was compressed between two parallel plexiglass plates.

For calculation of the mineral content we used the integrated area of the absorption curve under the reference level. This reference level (extra-osseous level) was defined as the average of 10 values at the beginning and 10 values at the end of the curve for both bones of the forearm. The reference level thus corresponded to the absorption through the water in the rubber cuff (fig. 2).

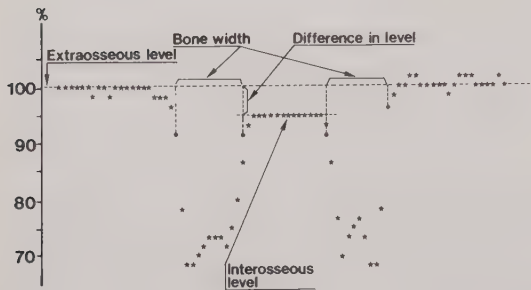


Figure 2. Some characteristics in the measurement procedure

The detector was connected to a digital ratemeter which in its turn was connected to a paper tape punch unit. Punched values were obtained every fourth second, corresponding to 0.67 mm of the scanning path. A special calculation programme was developed for evaluating the measurements by computer. The following information was obtained: bone width (W) for each bone of the forearm, bone mineral content (BMC) in g/cm and mean bone mineral content (BMC/W) in g/cm². BMC means, unless otherwise stated, the sum of measured mineral content in the four bones of both forearms and BMC/W means the average BMC/W in the four bones. With good fixation of the forearms the method has a reproducibility of about 2 %. (Lindergård et al., 1974).

A level was estimated for the absorption values between the two forearm bones. This was done after excluding six values nearest the ulnar edge of the radius and the radial edge of the ulna. The level obtained was called the interosseous level (fig. 2).

As a measure of the difference between the "extraosseous" and the "interosseous level" the logarithm value for the quotient between "extraosseous" and "interosseous level" was used. This value, called the difference in level, was lower in adipose individuals and in some of them it was even negative, suggesting the presence of fatty tissue between the bones with less photon absorption than through water. When the "difference in level" was used as a fat parameter the values were taken with opposite signs. The BMC was corrected for the "interosseous level" by subtracting from the total BMC the absorption area for each bone between the "extraosseous" and the "interosseous level". This corrected mineral content was designated the level-corrected BMC.

In adipose individuals an area was noted, close to the outer border of radius and ulna, which had lower photon absorption than water. Since it was indicated that the lower absorption was caused by fatty tissue this area was designated as fat hump (fig. 3). The size of the "fat hump" was calculated by multiplying the base by the height. Only the size of the "fat hump" adjacent to the radius was calculated since this one seemed to be more invariable and easier to define than that one adjacent to the ulna.

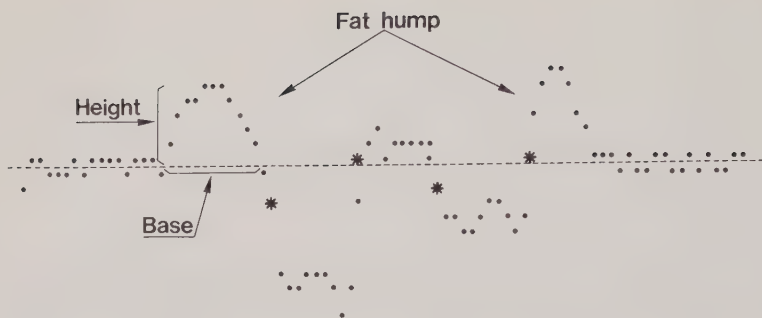


Figure 3 The absorption profile of fat tissue ("fat hump").

The following data were recorded: age, height, weight and forearm length measured from the tip of the olecranon to the tip of the processus styloides ulnae. The forearm length was calculated as the average length of both forearms. The body surface area was calculated by nomogram (DuBois and DuBois, 1916). The skin thickness was measured by a caliper (John Bull, British indicator, Ltd, England) over the brachioradial muscle, and the average value for both arms was used.

An attempt was also made to elucidate each individual's dietary habits, especially the intake of food containing calcium, such as milk, sour milk, yoghurt and cheese. Each individual had to answer a questionnaire concerning the state of health, including a question whether any arm had ever been injured. For information on tobacco consumption, drinking habits and physical activity a questionnaire was used as devised by the Swedish National Health Bureau. Questions about medication, and vitamin intake in particular were also included. The handedness was recorded according to a 5 point scale ranging from right-handedness to left-handedness. The number of births and the duration of lactation were recorded in the women.

Statistical calculations were carried out by linear correlation analysis, multiple correlation analysis and Student t-test.

RESULTS

The bone mineral content, BMC (g/cm) and the mean bone mineral content, BMC/W (g/cm^2) varied according to sex and age (figs. 4 and 5). The values were lower in females than in males and the 12-year-old children had considerably lower values than the adults. The measurement in the children group was not included in the following study, except for the recording of calcium intake.

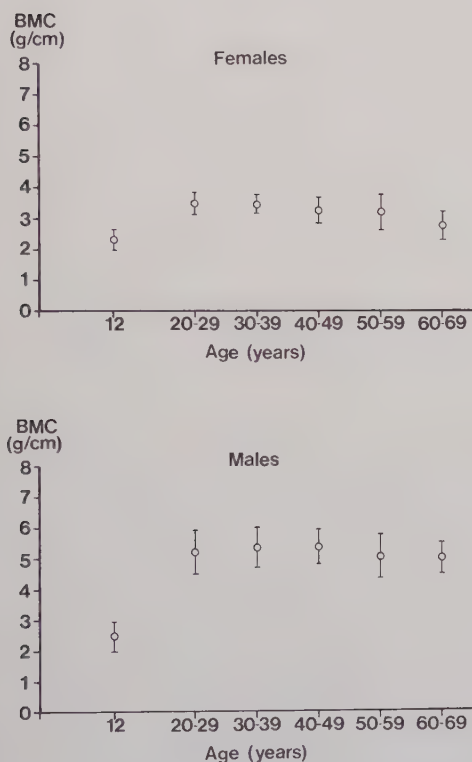


Figure 4. Bone mineral content, BMC (g/cm) ± 1 SD in a group of 12-year-old children and in adults.

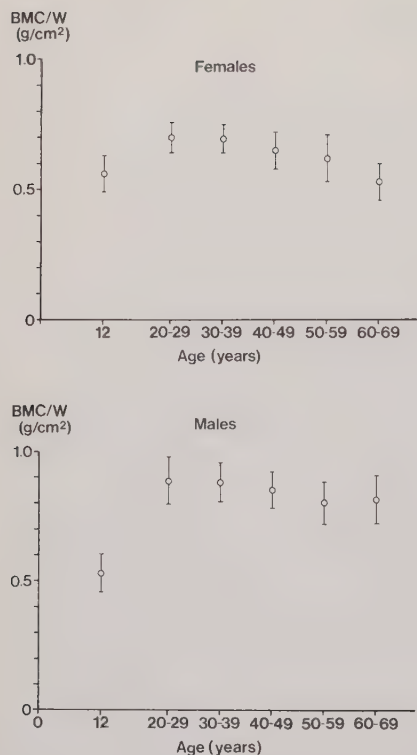


Figure 5. Mean bone mineral content, $\text{BMC/W (g/cm}^2\text{)} \pm \text{SD}$ in a group of 12-year-old children and in adults.

Various body parameters and their relation to BMC and BMC/W

The various body parameters (table I); body weight, body height, body surface area and forearm length, showed strong positive intercorrelations. Both BMC and BMC/W increased with increasing values of the different body parameters (table II). However, in the females the BMC and the BMC/W seemed to fall with increasing values of body weight and body surface. The BMC/W decreased with increasing age while the BMC was less affected by age.

Table I. Some characteristics in the body parameters, fat parameters and the BMC and BMC/W expressed as mean and coefficient of variation.

Age	Weight kg	Height cm	Body surface m ²	Forearm length cm	Fat hump %	Skinfold thickness mm	Diff. in level	EMI Wt/Ht ² x 1000	BMC g/cm	BMC/W g/cm ²
Women	20 - 29 N = 15	168 2.9 %	1.64 5.5 %	25.6 3.7 %	113 112.3 %	7.27 37.1 %	869 35.9 %	2.04 9.6 %	3.52 9.5 %	.703 8.7 %
	30 - 39 N = 11	163 2.7 %	1.64 5.2 %	25.0 3.2 %	157 53.5 %	8.15 26.8 %	770 38.7 %	2.26 14.8 %	3.51 8.4 %	.694 8.1 %
	40 - 49 N = 11	159 3.5 %	1.69 6.9 %	24.5 4.6 %	321 77.3 %	10.31 33.5 %	435 82.1 %	2.69 17.4 %	3.30 12.3 %	.645 10.7 %
	50 - 59 N = 11	160 3.4 %	1.72 6.8 %	24.9 4.2 %	288 52.7 %	11.05 29.4 %	444 91.0 %	2.73 18.4 %	3.25 17.6 %	.623 13.9 %
	60 - 69 N = 11	161 3.7 %	1.75 8.7 %	25.0 5.2 %	371 60.1 %	10.49 39.4 %	490 49.3 %	2.76 14.4 %	2.80 15.2 %	.532 13.6 %
	20 - 29 N = 15	182 3.8 %	1.96 5.9 %	28.5 4.4 %	56 156.5 %	5.71 26.6 %	1298 22.0 %	2.28 9.6 %	5.20 13.5 %	.884 10.1 %
Men	30 - 39 N = 22	179 3.9 %	1.98 8.2 %	28.6 4.6 %	136 66.4 %	7.09 32.6 %	1225 17.8 %	2.50 12.1 %	5.34 12.0 %	.880 8.4 %
	40 - 49 N = 13	179 2.9 %	2.01 7.6 %	28.6 2.9 %	148 81.5 %	7.96 33.8 %	1129 24.5 %	2.55 12.7 %	5.36 10.2 %	.852 8.1 %
	50 - 59 N = 17	175 2.7 %	1.94 5.9 %	28.3 4.3 %	119 91.5 %	7.81 39.9 %	1202 19.4 %	2.58 10.0 %	5.22 9.4 %	.801 9.9 %
	60 - 69 N = 10	174 4.6 %	1.92 9.0 %	27.9 4.9 %	149 79.1 %	6.44 19.2 %	1178 15.3 %	2.55 11.7 %	5.02 10.5 %	.814 11.0 %

Table II. Bone mineral content, BMC (g/cm) and mean bone mineral content, BMC/W (g/cm²) in distal forearms correlated to different body parameters in a sample of normal adults. The statistical significance is graded from no significance, $p > 0.05$ (NS) to highly significant $p < 0.001$ (xxx). Figures in parenthesis indicate the correlation coefficients.

	BMC (g/cm)			BMC/W (g/cm ²)		
	ALL	WOMEN	MEN	ALL	WOMEN	MEN
Number	136	59	77	136	59	77
Body weight	Pos xxx (+0,51)	Neg xx (-0,40)	Pos xx (+0,32)	Pos xxx (+0,36)	Neg xxx (-0,50)	--- NS (+0,18)
Body length	Pos xxx (+0,77)	Pos xx (+0,40)	Pos x (+0,26)	Pos xxx (+0,72)	Pos xx (+0,35)	Pos xx (+0,31)
Body surface	Pos xxx (+0,69)	--- NS (-0,24)	Pos xx (+0,35)	Pos xxx (+0,56)	Neg xx (-0,37)	Pos x (+0,26)
Length of forearm	Pos xxx (+0,79)	--- NS (+0,24)	Pos x (+0,27)	Pos xxx (+0,71)	--- NS (+0,18)	Pos x (+0,27)
Age	--- NS (-0,09)	Neg xxx (-0,52)	--- NS (-0,10)	Neg xxx (-0,30)	Neg xxx (-0,64)	Neg xxx (-0,40)
Width of radius, mean of both arms	Pos xxx (+0,76)	Pos x (+0,28)	Pos xxx (+0,38)	Pos xxx (+0,47)	--- NS (-0,21)	Neg x (-0,25)

The average radius width as measured with this technique could also be used as a body parameter. The width increased significantly with the increasing values of the aforementioned body parameters and with increasing age. Furthermore BMC increased with increasing radius width (table II) but only up to a bone width of 16 - 18 mm in men and 12 - 14 mm in women. Consequently, the BMC/W had a maximum at the same bone widths.

Parameters of fatty tissue and their relation to BMC and BMC/W

Four measures were used as parameters of fatty tissue, namely: "fat hump", skin thickness, negative values of "difference in level", and body mass index ($BMI = \text{weight/height}^2$) (table I). There were regular and strong intercorrelations between these parameters (table III). The "difference in level", however, showed a weaker correlation to the other parameters of fatty tissue in people above the age of 50 than below this age.

The "fat hump", skin fold thickness and negative values of "difference in level" showed increasing values with increasing body weight and body surface area, while they showed decreasing values with increasing body height and forearm length (table IV). The different correlations between fat and body parameters were more clear-cut in the separate female and male groups than in the total material.

The size of the fat parameters increased with increasing age, especially in the females (table I). For the parameter "difference in level" however, no further changes were observed above the age of 50. BMC as well as BMC/W decreased with increasing values of the fat

Table III. Intercorrelation between different parameters of fatty tissue in normal adults. The statistical significance is graded from no significance, $p > 0.05$ (NS) to highly significant, $p < 0.001$ (xxx). Figures in parenthesis indicate the correlation coefficients.

	"Fat hump"			Skinfold thickness			Body mass index		
	ALL	WOMEN	MEN	ALL	WOMEN	MEN	ALL	WOMEN	MEN
Number	135	58	77	135-136	58-59	77	135-136	58-59	77
"Difference in level", negative value of	Pos xxx (+0,70)	Pos xxx (+0,74)	Pos xxx (+0,52)	Pos xxx (+0,69)	Pos xxx (+0,72)	Pos xxx (+0,57)	Pos xxx (+0,35)	Pos xxx (+0,68)	--- Ns (+0,22)
"Fat hump"				Pos xxx (+0,70)	Pos xxx (+0,67)	Pos xxx (+0,65)	Pos xxx (+0,68)	Pos xxx (+0,79)	Pos xxx (+0,65)
Skinfold thickness							Pos xxx (+0,55)	Pos xxx (+0,66)	Pos xxx (+0,50)

Table IV. Parameters of fatty tissue correlated to different body parameters and to age in normal adults. The statistical significance is graded from no significance, $p > 0.05$ (NS) to highly significant, $p < 0.001$ (xxx). Figures in parenthesis indicate the correlation coefficients.

	"Fat hump"			Skinfold thickness			"Difference in level" negative value of		
	ALL	WOMEN	MEN	ALL	WOMEN	MEN	ALL	WOMEN	MEN
Number		58	77	136	59	77	136	59	77
Body weight	POS	POS	POS	POS	POS	POS	---	POS	---
	xxx (+0,30)	xxx (+0,77)	xxx (+0,57)	x (+0,22)	xxx (+0,68)	xxx (+0,43)	NS (-0,15)	xxx (+0,60)	NS (+0,20)
Body height	NEG	NFG	---	NEG	---	---	NEG	NFG	---
	xxx (-0,40)	xx (-0,36)	NS (-0,03)	xxx (-0,37)	NS (-0,26)	NS (-0,05)	xxx (-0,64)	xxx (-0,42)	NS (-0,02)
Body surface	---	POS	POS	---	POS	POS	NEG	POS	---
	NS (+0,04)	xxx (+0,61)	xxx (+0,42)	NS (0,00)	xxx (+0,58)	xx (+0,31)	xxx (-0,38)	xxx (+0,43)	NS (+0,15)
Length of forearm	NEG	---	---	NEG	---	---	NEG	NEG	---
	xxx (-0,35)	NS (-0,23)	NS (+0,09)	xxx (-0,31)	NS (-0,14)	NS (+0,07)	xxx (-0,62)	x (-0,28)	NS (+0,03)
Age	POS	POS	---	POS	POS	---	POS	POS	---
	xxx (+0,32)	xxx (+0,48)	NS (+0,20)	xx (+0,27)	xx (+0,40)	NS (+0,18)	x (+0,21)	xxx (+0,45)	NS (+0,19)

parameters (table V). The mineral content was influenced most clearly and consistently by the "difference in level", and least by the BMI.

BMC and BMC/W after correction for different fat parameters

It was apparent that both BMC and BMC/W were influenced by the "fat hump", the skin thickness and the "difference in level". Thus, the BMC and the BMC/W were corrected for these parameters. By correction for "fat hump" and skin thickness, the b-value was used in the equation for the correlation between mineral mass and a fat parameter in the total adult material ($BMC = a + b \times \text{"fat hump"}$ and $BMC/W = a + b \times \text{skin thickness}^x$). After correction for the "difference in level" the expressions "level-corrected BMC" and "level-corrected BMC/W" were used (see Methods).

Even after correction for a fat parameter (table VI), there remained an effect both on BMC and BMC/W of the various body parameters (table VII) which as expected, was more pronounced on the BMC than on the BMC/W. The effect of the different body parameters were now more uniform and the previously noted negative effect of weight and body surface among female disappeared.

- x) For the correlation between mineral content and "fat hump" the following applies, for example:
 $BMC = 4.94 - 0.00308 \times \text{"fat hump"}$. For a normal person with $BMC = 5.20$ and "fat hump" = 150 the mineral mass will be corrected to "fat hump" = 0. Thus $BMC \text{ corr.} = 5.20 + 0.00308 \times (150 - 0) = 5.66$.

Table V. Bone mineral content, BMC (g/cm) and mean bone mineral content, BMC/W (g/cm²) in distal forearms correlated to four different parameters of fat tissue in normal adults. The statistical significance is graded from no significance (NS) to highly significant, $p < 0.001$ (xxx). Figures in paranthesis indicate the correlation coefficients.

	BMC (g/cm)			BMC/W (g/cm ²)		
	ALL	WOMEN	MEN	ALL	WOMEN	MEN
Number	135-136	58-59	77	135-136	58-59	77
"Fat hump"	Neg xxx (-0.45)	Neg xxx (-0.51)	--- NS (-0.06)	Neg xxx (-0.49)	Neg xxx (-0.54)	--- NS (-0.07)
Skinfold thickness	Neg xxx (-0.42)	Neg xxx (-0.43)	--- NS (-0.07)	Neg xxx (-0.45)	Neg xxx (-0.42)	--- NS (-0.13)
Body mass Index	--- NS (-0.04)	Neg xxx (-0.49)	--- NS (+0.21)	Neg x (-0.17)	Neg xxx (-0.54)	--- NS (+0.02)
"Difference in level", Negative value of	Neg xxx (-0.76)	Neg xxx (-0.59)	Neg xx (-0.35)	Neg xxx (-0.74)	Neg xxx (-0.54)	Neg xx (-0.33)

Table VI, BMC and BMC/W corrected for different fat parameters and "level-corrected BMC" further corrected for two body parameters, expressed as mean and coefficient of variation.

	Age	BMC (g/cm), corrected for:			BMC/W (g/cm ²), corrected for:			"Level-corrected BMC" corrected to:	
		Fat hump	Skinfold thickness	Diff. in level	Fat hump	Skinfold thickness	Diff. in level	Ht=170 cm	Arm=27 cm
Women	20 - 29 N = 15	3.90 8.2 %	4.61 8.0 %	3.08 8.1 %	.750 7.1 %	.843 7.4 %	.614 7.6 %	3.24 10.2 %	3.57 9.5 %
	30 - 39 N = 11	3.99 8.1 %	4.74 8.9 %	3.12 7.3 %	.757 6.9 %	.851 7.2 %	.616 8.5 %	3.58 7.5 %	3.80 8.4 %
	40 - 49 N = 11	4.28 17.1 %	4.85 11.6 %	3.07 11.9 %	.773 13.8 %	.844 9.9 %	.602 11.3 %	3.83 13.4 %	3.94 13.0 %
	50 - 59 N = 11	4.14 15.3 %	4.92 9.7 %	3.01 13.0 %	.738 11.4 %	.836 9.1 %	.578 11.1 %	3.67 12.2 %	3.70 10.4 %
	60 - 69 N = 11	3.94 16.5 %	4.38 16.5 %	2.54 17.1 %	.680 13.4 %	.735 14.6 %	.483 15.8 %	3.17 15.1 %	3.23 19.5 %
	20 - 29 N = 15	5.37 12.4 %	6.06 11.4 %	4.43 12.8 %	.907 9.4 %	.995 8.7 %	.754 9.9 %	3.64 19.8 %	3.92 17.9 %
	30 - 39 N = 22	5.76 11.4 %	6.41 10.3 %	4.60 12.7 %	.934 7.9 %	1.016 7.4 %	.756 9.2 %	4.02 16.8 %	4.05 15.8 %
	40 - 49 N = 13	5.82 10.9 %	6.56 8.0 %	4.65 9.8 %	.907 9.5 %	1.006 8.2 %	.739 8.9 %	4.03 10.7 %	4.12 10.7 %
Men	50 - 59 N = 17	5.59 10.0 %	6.40 11.5 %	4.44 11.3 %	.849 9.8 %	.952 10.8 %	.681 12.0 %	4.09 10.8 %	4.00 12.9 %
	60 - 69 N = 10	5.48 14.2 %	5.99 10.1 %	4.30 12.0 %	.873 13.6 %	.938 10.6 %	.676 10.8 %	4.04 12.2 %	4.01 11.8 %

Mean bone mineral content, BMC/W (g/cm^2) corrected to some parameters of fatty tissue and correlated to different body parameters in normal adults. The statistical significance is graded from no significance, $p > 0.05$ (NS) to highly significant, $p < 0.001$ (xxx). Figures in paranthesis indicate the correlation coefficients.

Table VII.

	"Fat hump"-corrected BMC/W (g/cm^2)			Skinfold corrected BMC/W g/cm^2			"Level-corrected BMC/W" (g/cm^2)		
	ALL	WOMEN	MEN	ALL	WOMEN	MEN	ALL	WOMEN	MEN
Number	135	58	77	136	59	77	136	59	77
Body weight	Pos xxx (+0.57)	--- NS (+0.18)	Pos xxx (+0.43)	Pos xxx (+0.51)	--- NS (-0.01)	Pos xxx (+0.39)	Pos xxx (+0.38)	Neg x (-0.31)	--- NS (+0.22)
Body length	Pos xxx (+0.60)	--- NS (+0.05)	Pos x (+0.27)	Pos xxx (+0.62)	--- NS (+0.18)	Pos x (+0.26)	Pos xxx (+0.65)	--- NS (+0.21)	Pos xx (+0.30)
Body surface	Pos xxx (+0.66)	--- NS (+0.19)	Pos xxx (+0.43)	Pos xxx (+0.63)	--- NS (+0.05)	Pos xxx (+0.40)	Pos xxx (+0.54)	--- NS (-0.23)	Pos xx (+0.29)
Length of forearm	Pos xxx (+0.62)	--- NS (-0.03)	Pos xx (+0.29)	Pos xxx (+0.64)	--- NS (+0.08)	Pos x (+0.28)	Pos xxx (+0.64)	--- NS (+0.08)	Pos x (+0.27)

BMC and BMC/W after correction for one fat parameter and one body parameter

Since there remained an influence of the body parameters even after the BMC and the BMC/W had been corrected for one of the fat parameters, the BMC and the BMC/W were also corrected for one of the body parameters. These corrections were regarded as meaningful only where the b-values were similar in the two sexes in the correlation between corrected BMC and a body parameter e.g. height or arm length. Table VI shows two examples where these further corrections have been performed.

Mineral content in distal forearm in relation to right- and left-handedness

Out of the 136 adult persons, 78 considered themselves right-handed, 40 mainly right-handed, 10 ambidextrous, 5 mainly left-handed and 3 left-handed.

There was a good correlation between the mineral mass in right and left forearm both for the unit BMC ($r = 0.97$) and for the unit BMC/W ($r = 0.95$). There was, however, a positive difference in BMC between right and left forearm for the group of pronounced right-handers, whereas this difference was not significant for other groups of handedness (fig. 6). In these groups, however, the number of individuals were smaller.

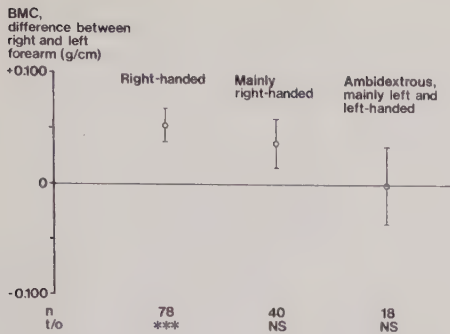


Figure 6. Difference in BMC (g/cm) $\pm$ 1 SE for different-handedness, t/0 signifies the Student t-value for the deviation from zero.

Since it was assumed that the difference in BMC might be due to varying quantities of fatty tissue in the forearms, the difference was also calculated between the size of a fat parameter in right and left forearm. The "fat hump" was not significantly larger in either arm, while both skin thickness and negative values of "difference in level" showed larger value in the left than in the right arm in the group of pronounced right-handers (fig. 7).

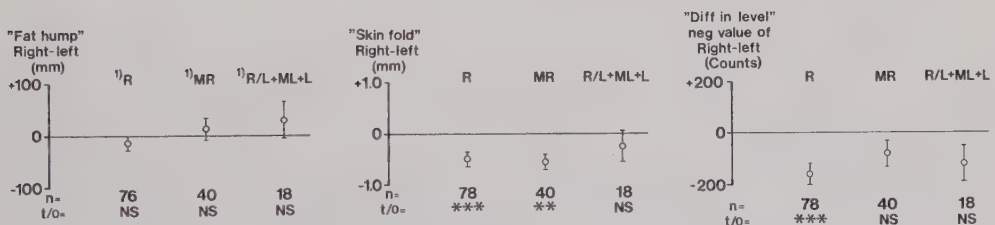


Figure 7. Difference in the size of three fat parameters $\pm$ 1 SE between right and left forearm in normal adults.

1) R = right-handed, MR = mainly right-handed,
R/L = ambidextrous, ML = mainly left-handed and
L = left-handed.

There was also noted a greater forearm circumference in the right forearm in the group of pronounced right-handers. When the comparison of BMC in right and left forearm without correction for fat was replaced by the "level-corrected BMC", there remained no significant difference for any kind of handedness (fig. 8).

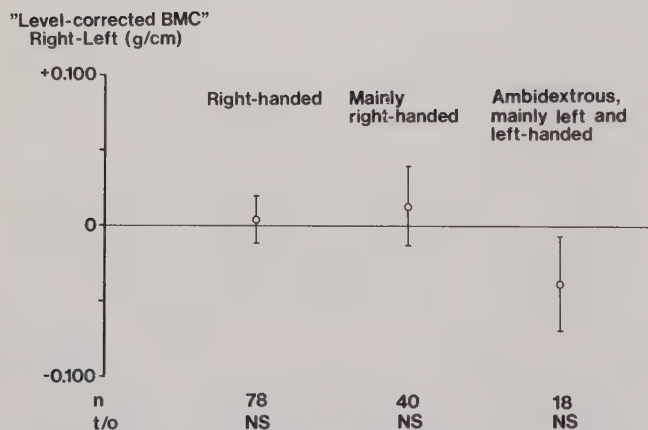


Figure 8. "Level-corrected BMC" (g/cm) $\pm$ 1 SE, difference between right and left forearm in normal adults with different handedness.

Mineral content in relation to: dietary habits, physical exercise, number of pregnancies, duration of lactation, smoking, alcohol consumption and medication.

For comparison of the mineral mass between different groups of individuals the unit of "level-corrected BMC/W" was used. This unit seemed more correct to use than a fat-corrected BMC/W calculated from the total material.

Dietary habits

The intake of calcium-containing food was estimated solely from the intake of milk products, and was expressed in grams of calcium per day. The "level corrected BMC/W" showed higher values with higher calcium intake ($r = 0.24$, $p < 0.01$). However, it was noted that the calcium intake clearly decreased with increasing age (fig. 9) ($r = 0.45$, $p < 0.001$). After elimination of the effect of age on the mineral content there remained no significant correlation between the "level-corrected BMC/W" and the calcium intake. On the other hand a correlation did remain between "level-corrected BMC/W" and age even after elimination of the calcium intake ($r = -0.24$, $p < 0.02$).

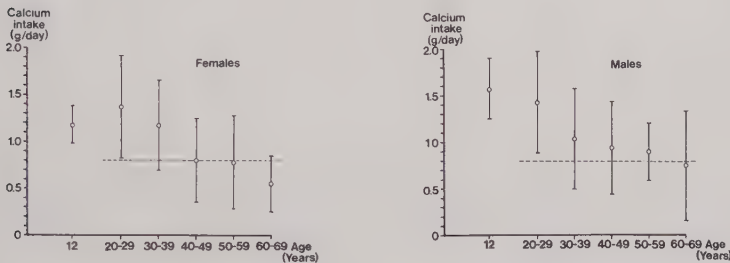


Figure 9. Calcium intake in children and adults estimated from milk products only, mean ± 1 SD, in different age groups. Dotted line indicates recommended intake of calcium in g/day.

Physical exercise

Sixtynine persons claimed that they had a work with relatively little physical activity (grade 1-2) whereas 67 persons had a work with heavier physical activity (grade 3-4). In the males heavier types of work was more often reported in the group ≥ 50 years of age than in the group < 50 . No significant difference in "level-corrected BMC/W" was found between any of the groups (table VIII).

Table VIII. "Level-corrected mean bone mineral content" (g/cm) in normal adults related to different grades of occupational and leisure physical activity.

	Occupational physical activity				Leisure physical activity			
	Grade 1 - 2		Grade 3 - 4		Grade 1 - 2		Grade 3 - 4	
	Women	Men	Women	Men	Women	Men	Women	Men
Number	25	44	34	33	21	29	38	48
"Level-corrected BMC/W" (g/cm ²)	0.596	0.730	0.570	0.720	0.561	0.736	0.592	0.720
± 1 SD	±0.065	±0.077	±0.084	±0.084	±0.063	±0.069	±0.083	±0.086

Number of childbirths and duration of lactation

Nineteen women were childless, 12 had given birth to one, 19 to two, 5 to three and 4 had given birth to 4 or more children. Comparison by pairs in the different decades showed no difference (table IX). Twenty women had not breast-fed their children, 16 had breast-fed for 1-4 months, 12 for 5-8 months, 5 for 9-12 months, 2 for 13-16 months and 4 $\geq$ 17 months. No correlation was found between BMC and duration of lactation (table IX).

Table IX. "Level-corrected mean bone mineral content" in adult women related to number of childbirths and to months of lactation.

	Number of childbirths					Months of lactation					
	0	1	2	3	≥ 4	0	1-4	5-8	9-12	13-16	≥ 17
Number	19	12	19	5	4	20	16	12	5	2	4
"Level-corrected BMC/W" (g/cm ²) ± 1 SD	0.598 ±0.080	0.594 ±0.059	0.562 ±0.065	0.581 ±0.114	0.553 ±0.123	0.597 ±0.078	0.567 ±0.067	0.610 ±0.068	0.563 ±0.092	0.509 ±0.064	0.525 ±0.098

Smoking

The influence of cigarette smoking on BMC was also studied. The normal sample was divided into three groups: 49 persons stated that they had never smoked any form of tobacco, 44 persons had smoked 5 cigarettes or more daily during the last 5 years, and 18 persons had smoked 15 cigarettes or more daily during the last 5 years. The incidence of smoking was evenly divided between different age groups and between the sexes. The "level-corrected BMC/W" for the different groups is shown in table X. There were no significant differences.

Table X. "Level-corrected mean bone mineral content" (g/cm²) in normal adults related to different grades of cigarette smoking.

	Number	"Level-corrected BMC/W" (g/cm ²) ± 1 SD
No smoker	49	0.640 ± 0.115
≥ 5 cig/day	44	0.645 ± 0.107
≥ 15 cig/day	18	0.684 ± 0.110

Alcohol and medication

The influence of alcohol and drugs on mineral content was inconclusive.

DISCUSSION

As expected, the bone mineral content, BMC (g/cm), increased with the increasing values of the body parameters studied: weight, body surface, height and forearm length. Exceptions were the females who showed decreasing BMC with increasing body weight and surface area. Thus, if the unit BMC (g/cm) is to be used as a measure of mineral mass, this should be corrected for one of the above body parameters.

The unit mean bone mineral content, BMC/W (g/cm^2), is the mineral content corrected for the body parameter bone width. Many authors have preferred to use this unit for the comparison of mineral content between normal and sick individuals (Johnston, Smith, Pao-Lo Yo & Deiss, 1968; Goldsmith, Johnston, Ury, Vose & Colbert, 1971; Nilsson & Westlin, 1973; Levin, Boisseau & Avioli, 1976; and others).

In this study it was noted that the BMC/W also varied with the size of different body parameters. The females showed deviating results here as well, with falling values of BMC/W when weight and body surface area increased. The BMC/W also decreased with increasing age.

It is known that metacarpal cortical width decreases in normal aging at the same time as the exterior diameter of the metacarpal bones increases somewhat (Horseman, 1976). In this sample of normals, it could be shown that also the width of the radius increased with increasing age. The radius width thus behaved differently from the other quantity parameters.

As a consequence, the BMC increased with greater bone width only to a maximum value, after which the age dependent decrease of BMC became discernible. For the same reason, the BMC/W increased to a corresponding maximum value, and then decreased. This different behavior of bone width compared to the other body parameters could also explain why BMC/W decreased more with age than did BMC.

To correct for another body parameter which does not vary with age as does the bone width is, however, also difficult as the correlations of BMC to these other body parameters were so different in the two sexes.

The negative correlation between BMC and BMC/W respectively and weight and body surface area in the females, together with the observation that the "fat hump" was bigger in overweight women, resulted in further studies on how different parameters of fatty tissue affected the evaluation of mineral mass.

It seemed natural that the "fat hump" was caused by fatty tissue, since fatty tissue has a lower attenuation coefficient than water and soft tissue (Hubbell, 1969) and therefore produces a rising photon absorption profile with our method (fig. 3). Air in the water-filled rubber cuff could give a similar profile, but this source of error could be excluded. The "fat hump" also showed a strong positive correlation to the remaining three fat parameters: skin thickness of forearms, BMI (weight/height²) and "difference in level".

In anthropological literature various indexes of adiposity have been discussed. One of the most reliable measures seems to be the Body Mass Index, BMI (Khosla & Lowe, 1967; Keys, Fidanza, Karvonen, Kimura & Taylor, 1972). This index also correlated well with other fat parameters.

The photon absorption between radius and ulna, here designated the "interosseous level", was displaced upwards in adipose persons, thus approaching the water level (= "extraosseous level") (fig. 2). The difference between the water level and the "interosseous level" was also considered a parameter of fatty tissue. This so-called "difference in level" also correlated well with other fat parameters.

As was expected the fat parameters showed lower values in persons of big body height and forearm length, while the fat parameters increased with increasing weight and body surface. It is well known that the quantity of adipose tissue increases with increasing age (Khosla & Lowe, 1967). Here it could be shown that not only conventional parameters of fatty tissue such as the skin thickness and the BMI increased with age, but also the "fat hump" and "difference in level". It finally became apparent that both the BMC and the BMC/W decreased with increasing values of the different fat parameters. This was most clear-cut in the females, probably due to their higher values of the fat parameters.

The adipose tissue thus seems to give a false impression of low mineral mass values. The reason is probably that in our method we used photon absorption through the water-filled rubber cuff round the forearm as a reference level for the absorption by the bones. Thus, either another reference level must be used or the mineral content must be corrected for one of the fat parameters.

The Norland-Cameron instrument (Norland Instruments, Wisconsin, USA) uses as a reference level a point just ulnar to the radius and thus lying between the bones. This reference level corresponds very closely to the "interosseous level" in this study, but here the reference level is not a point but the greater portion of the area between the bones. West and Reed, 1968, in femoral measurements, have used the relatively large area of soft tissues in this region as a reference level. In both these methods fatty tissue is excluded as a direct source of error. Our method can easily be adapted to use the "interosseous level" as a reference level instead of the water level ("extraosseous level"). When measuring

on the midshafts of the forearms and using our method of fastening the arm, the distance between radius and ulna is large enough to give values with a small scatter. In our study the coefficient of variation for the absorption values between the bones ("interosseous level") was 0.76 ± 0.26 %. When using the "interosseous level" as a reference level instead of the water level ("extra-osseous level") "levelcorrected BMC" or "level-corrected BMC/W" were obtained. If measurements are made more distally on the forearms fat correction cannot be made with the "interosseous level" since the space between the bones becomes too small. An alternative would be to place a reference level within the upper limit of the "fat hump" (fig. 3), but this area shows considerably larger scatter than the relatively even level between the bones.

It should, however, be pointed out that if the photon absorption between the bones is to be used as a reference level, an increased density in this area can give a false impression of low mineral mass in the skeleton. The soft tissue absorption, here designated "difference in level", correlated well in this material with the "fat hump", skinfold thickness and BMI among younger subjects (20-49 years) while the corresponding correlation was less certain among older ones. The soft tissue absorption depends on fatty tissue in 62 % ($r = 0.79$) for women in the age group 20-49, and in only 29 % ($r = 0.54$) in the age group 50-69. Thus, in the latter age group an additional factor influences the soft tissue photon absorption. If the group of women aged 40-49 is compared to those aged 60-69 the following ensued (table I): The size of the "fat hump" increased with 16 %, the skinfold thickness increased with 2 % and the BMI with 3 % while the soft tissue absorption between the bones also increased with 13 %.

If the soft tissue absorption was due to fatty tissue in a corresponding degree in older as in younger women the soft tissue absorption should instead decrease with 16, 2 or 3 % respectively. The deviation between the observed and expected decrease in soft tissue absorption was then 29, 15 or 16 %. Meanwhile it can be concluded that the uncorrected BMC in the corresponding age groups decreased with 15 % and the BMC/W with 18 %. The interpretation could be that the loss in mineral mass that occurs in older women is deposited in the soft tissue.

An increased amount of calcium in soft tissue in the forearms of elderly people could also contribute to the greater decrease in mineral content with age for "level-corrected BMC" and "level-corrected BMC/W" than for mineral mass corrected for some of the other fat parameters and also for uncorrected mineral mass. Perhaps it could also help to explain why the mineral mass seems to decrease more in older women measured with Cameron-Norland instruments (Mazess & Cameron, 1973) than with ours. Of course it is very important, when different normal materials are to be compared, if the reference level is the photon absorption through water or the tissue between the bones.

It should further be pointed out that soft tissue calcification, when identified by microscopic examination of autopsy material, could be found in 79 % of patients on regular hemodialysis and that calcification was regarded to be severe in 36 % (Kuzela, Huffer, Conger, Winter & Hammond, 1977). If soft tissue calcification is also located between the bones in the forearms of hemodialysis patients a false low mineral content could be measured, if the soft tissue absorption is used as a reference level.

Instead of the aforementioned reference levels the relationship between one of the fat parameters and the mineral content could be used as a correction factor.

The differences, however, between the two sexes were large both with regard to the size of the different fat parameters and to the uncorrected mineral mass. Furthermore, there was a strong influence of age on the mineral content especially among women above 50 years of age. Therefore, it seems unjustified to group the two sexes together. To use a correction factor calculated for each sex was also difficult, since the influence of fatty tissue on BMC was less clear in the males. Possibly a larger material could give better information.

The negative influence of fatty tissue on measured mineral content has also been observed by others (Sorenson & Mazess, 1970; Zeitz, 1972; Wooten, Judy & Greenfield, 1973), but more from an experimental point of view.

Even after correction for a fat parameter there was a positive correlation between BMC and the body parameters, but this correlation was less pronounced and the negative correlation between BMC and body weight in women could no longer be shown.

No matter how the mineral content was corrected, the mineral content was lower in women than in men, and the BMC decreased significantly in women above the age of 50. Furthermore, there was a greater scatter of the BMC values in older women than in younger in agreement with the view that post-menopausal women consist of two populations as far as osteoporosis is concerned (Jurist, 1970).

Comparison of BMC between dominant and non-dominant arms showed that the quantity of fat was once more a source of error. Higher values for adipose tissue were measured in the non-dominant arm, and consequently BMC values became higher in the dominant. After correction for a fat parameter, this difference disappeared. Thus, it was not possible to show any real difference in mineral mass between the dominant and non-dominant forearm.

The mineral mass in the forearm seemed to increase with increasing intake of calcium, here estimated from the intake of milk products. Since, however, the intake of milk products decreased markedly with age, the final correlation was less certain. It was, however, interesting to note that even within one age-group, men above 60 years, there was a clear correlation between intake of milk products and mineral mass ($p < 0.001$). The material is small, however, and even if milk products are considered to be our most important source of calcium (Nordin, 1976), the relation to other calcium products has not been studied here.

No correlation could be shown between mineral mass and physical activity, number of pregnancies, duration of lactation, smoking, alcohol intake or intake of medicine. The groups may be too small, but since there were no trends it is not probable that the mineral mass in cortical bone varies with the above mentioned factors in a normal population.

In conclusion, it was shown that the BMC measured with photon absorptiometry showed strong positive correlations to different body parameters but it was difficult to correct the measured values for these parameters. Fatty tissue was shown to be a source of error and should always be corrected for.

In practice, we use the standard BMC when following the development in the same individual. If the individual's adipose tissue significantly changed in amount during the period, correction is performed using the b-value in the correlation between BMC and the size of the "fat hump".

When an individual's mineral content is to be compared with that of normals or other groups of patients, we use the standard BMC/W corrected for the size of the "fat hump".

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Changes in bone mineral content evaluated
by photon absorptiometry before the start
of active uremia treatment.

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Abstract. Bone mineral content (BMC) in the forearm was evaluated by photon absorptiometry in 74 patients out of 198 started on active uremia treatment during 1973 - 1979. The BMC was measured repeatedly up to 24 months prior to and 15 months after the start of regular hemodialysis (RDT). The mean change per month, was - 0.43 % before the start and + 0.08 % after the start, showing that RDT-patients have low BMC chiefly because they lose mineral before the start of active uremia treatment. Patients not given extra calcium and/or vitamin D seemed to lose mineral faster than those given this medicine. The mineral content was lower in patients with polycystic kidney disease than in patients with glomerulonephritis.

It has been known for a long time that uremic patients suffer from poor mineralization of the skeleton. This has been studied by photon absorption, histological, radiological and other techniques (David et al. 1977). Most of the studies by photon absorptiometry, neutron activation analysis and x-ray spectrophotometry have been performed on patients undergoing regular hemodialysis treatment (RDT) and have usually revealed low or decreasing bone mineral content (BMC) (Atkinson et al. 1973, Dalén and Alvestrand 1973, Catto et al. 1973, Griffiths et al. 1973, Diamond et al. 1976, Overton and Silverberg 1976, Parfitt et al. 1976, Samizadeh et al. 1977, Kuhlencordt and Ringe 1978, Madsen et al. 1978, Rickers et al. 1978).

In our clinic it was confirmed that not only is the BMC low at the start of RDT but also that it remains relatively unchanged during the first years thereafter (Lindergård 1980).

It was therefore considered important to investigate the possibility that a great loss of bone mineral occurred already before the start of active uremia treatment and if so to try to identify factors effecting this change.

Material

During the years 1973 - 1979, 198 non-diabetic and non-neoplastic adult patients (≥ 20 years) were started on active uremia treatment, of whom 164 were given RDT and 34 had a kidney transplant without previous hemodialysis. In 74 of these 198 patients BMC was evaluated with photon absorptiometry both around the start of active uremia treatment and at least once during a period of from 3 to 24 months before the start. All patients who were subjected to a measurement in this way were included except one who was extremely obese, causing problems in the measuring procedure. The transplanted patients were studied only before transplantation.

The mean age, 47.5 ± 11.7 years, of the patients included in this study did not differ from the age of all patients started on active uremia treatment, 46.3 ± 11.9 years, nor were there any significant differences in diagnosis or sex.

Methods

The BMC was measured by a photon absorption technique as first described for clinical use by Cameron and Sorenson (1963) and later modified by us (Nauclér et al. 1974, Lindergård et al. 1974).

Measurements were made on the midshaft of the non-fistula arm between the distal and 2nd distal quarter of the length of the arm between the ulnar styloid process and the olecranon.

Correction of BMC for fat tissue was made with regard to the size of a fat hump laterally to the radius bone in the photon absorption profile (Lindergård 1981).

In the longitudinal study the standard BMC expressed in g/cm was used and when comparisons with normal were made, the standard BMC/W (BMC divided by bone width) expressed in g/cm^2 was used.

As the basal value was taken the mean value of measurements made within ± 2 months from the start of RDT or within 2 months before renal transplantation. From this zero start value deviations were counted in per cent backwards and forwards in time. One or two linear regression lines were calculated for each individual studied for at least 5 months before or after the start of active uremia treatment. The b-value in this equation expressed the change in BMC in per cent per month.

Comparisons between different groups were made using paired or unpaired t-test.

Results

On the 74 patients included in this study, 140 measurements of BMC were made before the start of active uremia treatment, 148 measurements around the start, and on 50 patients 184 measurements were also made after the start of RDT (Fig. 1). BMC increased in only 10 out of 74 patients before active uremia treatment, in all the others the mineral content decreased. The mean b-value for 64 patients studied for 5 months or more before the initiation of uremia treatment was -0.43% per month which is significantly different from zero ($p < 0.001$).

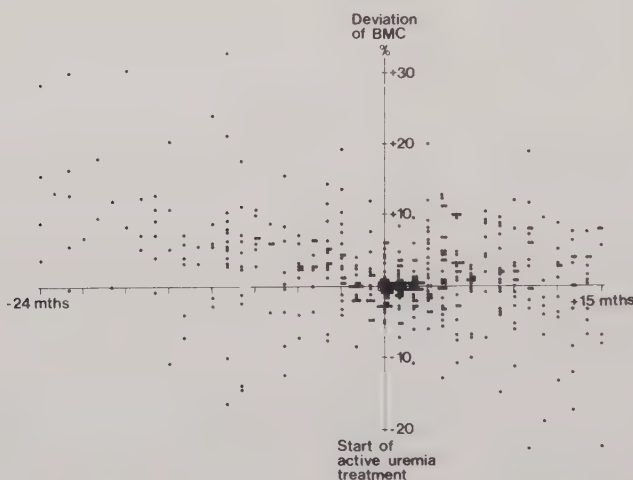


Figure 1. Bone mineral content (BMC) expressed in per cent change from the start of active uremia treatment. One dot represents one measurement.

Thirtyfive patients were followed-up both ≥ 5 months before and after the start in RDT. In this group of patients the mean b-value was -0.46% per month before the start and $+0.08\%$ per month after, which is a significant difference ($p < 0.01$) (Fig. 2).

Patients given extra calcium and/or vitamin D during the last half year before the start of active uremia treatment seemed to lose mineral slower than patients not given extra calcium or vitamin D ($p < 0.05$) (Fig. 3).

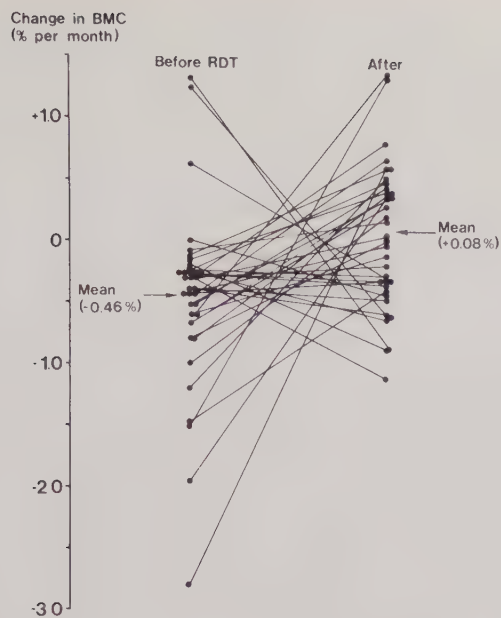


Figure 2. The change in BMC in 35 patients observed both before and after the start in regular hemodialysis.

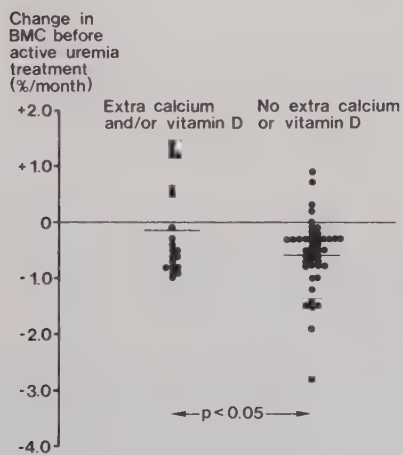


Figure 3. Change in BMC before the start of active uremia treatment in patients given extra calcium and/or vitamin D and in patients not given extra calcium and/or vitamin D.

There were no differences between the sexes in the speed of the mineral loss. Neither could the loss be correlated to the mean blood hemoglobin, mean serum creatinine, mean serum urea, mean serum calcium or mean serum phosphate during the year before the start of active uremia treatment, nor could any differences be seen between different renal diseases or between patients on protein reduced diet or on ordinary diet. There was a tendency in patients ≥ 50 years of age to lose mineral faster than younger ones, but the difference was not significant ($p < 0.10$).

The mineral content (BMC/W , g/cm^2) at the start of active uremia treatment expressed in the number of standard deviations from normal was significantly below zero in the whole group of patients (-0.84 ± 1.20 SDs, $p < 0.001$). There were no differences between the two sexes, different age groups or between patients given extra calcium and/or vitamin D or not.

Patients with polycystic kidney disease had lower BMC/W than patients with glomerulonephritis ($p < 0.025$) and there was also a tendency for patients with interstitial nephritis to have a lower mineral content than patients with glomerulonephritis ($p < 0.10$) (Fig. 4).

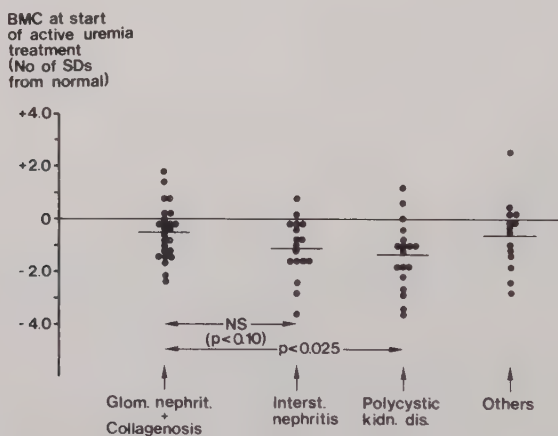


Figure 4. BMC/W at the start of active uremia treatment in four diagnosis groups.

Discussion

In 1973 it was our intention to measure the BMC in all patients with progressive uremia. However, only 74 out of 198 patients later accepted for active uremia treatment were measured during a long enough period to be included in this study. The main reason was that most patients came to our clinic too late. The selected group can, however, be regarded as representative of the whole group as far as sex, age and renal diagnosis are concerned.

Evaluation of bone mineral content (BMC) with photon absorptiometry is a well-established technique used all over the world and which has proved to be especially valuable in uremic patients. In our setting the precision is good with a coefficient of variation of about 2 % when measuring on both arms (Lindergård et al. 1974). In this study, however, two measures have been found necessary, both resulting in a somewhat reduced precision. Firstly only measurements performed on the non fistula arm were included in the study.

The reason was the observed greater loss of BMC in the fistula arm during the first months after the fistula operation compared with the other arm. Why this happens is unclear but may be due to decreased use of the arm after the surgical trauma. This factor seems to be of greater magnitude than the stimulation to increase in mineral content caused by the increase in the venous pressure (Deysine 1973). Secondly, correction for fat tissue was necessary as in a previous study we have shown that the measured BMC is falsely reduced by fat tissue in the arm when this and similar techniques are used (Lindergård and Naversten 1978).

In order to establish a parameter for the change in BMC the b-value in the regression line was chosen. This expresses the change in per cent per month from the start of active uremia treatment. In a few cases the decrease in BMC was especially fast during the last months before treatment. Hence only patients followed-up for at least 5 months were used when calculating the straight line equation. The mean decrease for these patients was 0.43 % per month. In 9 patients a sufficient number of measurements were made to give significant individual regression lines. In 8 of them, the slope was negative with a mean value of - 0.65 % per month and in one patient positive (+ 1.22 %). This patient was the only one who was parathyroidectomized before active uremia treatment. She was also given extra calcium and vitamin D.

The few longitudinal studies of BMC carried out by photon absorption or

neutron activation techniques before the start in active uremia treatment all concern small series with few measurements, and none has observed the BMC up to the start of dialysis or transplantation or thereafter. Madsen et al. (1978) measured on 10 non-dialysis patients with chronic renal failure twice but did not present this group separately. Overton and Silverberg (1976) studied 26 pre-dialysis patients and noted a negative "trend" in five but no significant decrease. Hosking and Chamberlain (1973) observed 14 patients and noted a decrease in BMC in 5 patients. Finally, Griffiths et al. (1973) reported on 7 patients all of whom demonstrated a rapid loss of BMC.

Our study thus seems to be the only one so far performed which clearly demonstrates a progressive loss of BMC in individual patients before the start of active uremia treatment. After the start of RDT the decrease seems to be arrested. Samizadeh et al. (1977) measured on 58 patients with different serum creatinine levels in a cross-sectional study and were able to correlate the bone mineral content both to the degree of uremia and to its duration which is in accordance with this study. However, these authors found an even stronger correlation to duration of uremia in RDT-patients. In another cross-sectional study on 26 pre-dialytic patients (Kuhlencordt and Ringe 1978) the BMC was low and the authors suggested that the essential mineral loss occurred before the start in dialysis. The reason why the loss of mineral ceased at the start of RDT in our study is uncertain but may be due to the relatively high calcium content of 1.75 mmol/l in our dialysis fluid.

Of the different parameters studied that may influence the speed of mineral loss only patients above 50 years of age (trend) and those not given extra calcium and/or vitamin D did worse than others. The group treated with 20 g protein-reduced diet had the same speed of mineral loss as those on an ordinary diet. However, of the 20 patients on this diet, 14 were also given extra calcium and/or vitamin D. In the small group of patients who were on a diet without extra calcium and/or vitamin D some lost bone mineral very quickly with a maximal loss of 2.8 % per month during 11 months, but the group was too small to allow statistical evaluation.

As a probable consequence of the mineral loss before active uremia treatment, the absolute mineral content (BMC/W), as compared to normal, was low at the start. The BMC/W was especially low in patients with polycystic kidney disease which is in contrast to the observation of Moorhead et al. (1974) who in an x-ray study noted less skeletal changes in poly-

cystic kidney patients on RDT. It is, however, in accordance with a newly performed histological study from this clinic on patients on RDT showing an increase in osteoid in patients with polycystic kidney disease or interstitial nephritis (unpublished observations). In that study we suggested that the reason was poor production of the active metabolite $1.25-(OH)_2-D_3$. Another reason may be the longer duration of pre-dialytic uremia in patients with polycystic kidney disease and interstitial nephritis, since these diseases have a slower progress than chronic glomerulonephritis.

If the low BMC/W is caused by a linear fall before the start of active uremia treatment, the slope of the regression lines can be used to calculate the point of time when BMC/W was normal (Fig. 5).

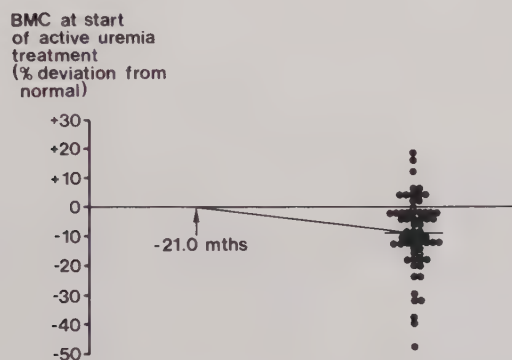


Figure 5. Calculated starting point of BMC loss before active uremia treatment.

In conclusion, the low bone mineral content observed in patients on active uremia treatment seems to be due to a loss before the start. In order to prevent this loss, active uremia treatment should either be started earlier or the loss should be treated with suitable drugs. A hint is given in the observation that patients given extra calcium and/or vitamin D lost mineral more slowly than those not given this supplementation but at the same time it should be kept in mind that potent vitamin D metabolites can deteriorate the kidney function (Christiansen et al.1978).

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CLINICAL EVALUATION OF BONE-DENSITOMETRY IN PATIENTS WITH FINAL RENAL INSUFFICIENCY OPERATED FOR HYPERPARATHYROIDISM

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Abstract. Because of difficulties in evaluating bone mineral mass with conventional methods in patients with final renal insufficiency before and after parathyroidectomy, bone densitometry has been tried. During a three year period ten patients have been selected for surgery. The parathyroidectomy performed was total in nine patients and subtotal in one. Bone mineral mass was significantly lower preoperatively in the operated patients than in other patients on regular hemodialysis and also lower than in a normal material. In four of ten patients there was a transient decrease in bone mineral mass after parathyroidectomy. Thereafter there was a significant increase in five of ten patients and in the whole group of patients. Thus bone densitometry was found to be of value in following patients with renal insufficiency selected for parathyroidectomy.

Bone demineralization is a common complication in final renal insufficiency. This so called renal osteodystrophy is partly due to osteomalacia which in turn is a result of a vitamin D resistance and partly due to reactive hyperparathyroidism. Surgical treatment of reactive hyperparathyroidism was first advocated by Stanbury, Lumb & Nicholson, 1960. Several authors have since reported favourable results with surgical treatment (e.g. Wilson, Hampers, Bernstein, Johnson & Merrill, 1971; Gordon, Coburn & Passaro, 1972; Hubertus & Loewe, 1972; Ogg, 1973; Finch & Jacobs, 1974; Popowniak, Esselstyn & Nakamoto, 1974) but there is considerable difficulty in selecting patients for surgery and in controlling the result. Bone demineralization can be judged from clinical symptoms such as bone pains and tendency to spontaneous fractures. The demineralization is also reflected in inorganic serum

phosphorous and calcium levels and in changes in alkaline phosphatases.

Important histopathological signs of renal osteodystrophy can be obtained by bone biopsy (Eastwood, Bordier & deWardener, 1973; Ritz, Krempien, Mehls & Malluche, 1973; Peart & Peart, 1973) but the examination is of limited value because it cannot be repeated as often as wanted. In routine clinical use X-ray examination of the skeleton is the most common method. The disadvantage of this method is the relative insensitivity and the difficulty of quantitating the lesion. There is thus a need for better and more harmless diagnostic procedures in the evaluation of bone-mineralization.

Photon absorption technique as first described by Cameron & Sorensen in 1963 has been widely used during recent years especially in hemodialysis centers in order to provide a measure of bone mineral mass.

The purpose of this investigation was to evaluate the clinical applicability of bone densitometry in patients undergoing surgical treatment for reactive hyperparathyroidism. We were thus interested to see whether bone densitometry values could be used to preoperatively select patients for surgical treatment and to follow the postoperative bone mineralization process.

METHODS

Bone mineral mass was evaluated with gamma-ray-densitometry. This method as first described for clinical use by Cameron & Sorenson in 1963 has then been modified in different ways. The apparatus used in this study is modified by Lindergård (Lindergård, Lindholm & Naver-

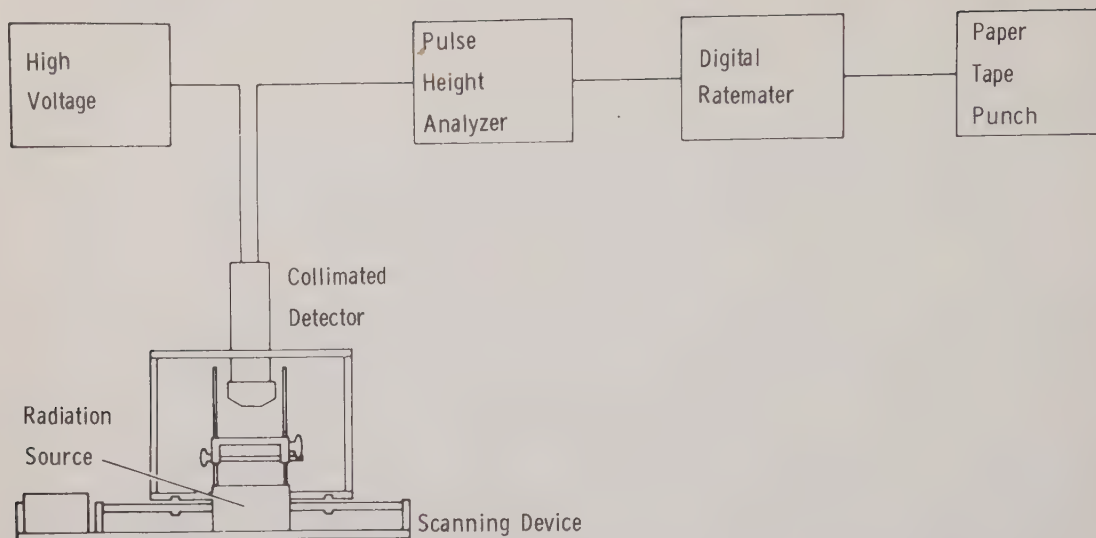


Fig. 1. Outline of the measurement procedure.

sten, 1974) after that described by Nauc  r, Nilsson & Westlin in 1974. A scheme of the arrangement of instruments is depicted in Fig. 1. Mineral mass was calculated as the sum of mineral mass in the four bones of both forearms from one scan on each arm, six cm proximal to the ulnar styloid process and expressed in g/cm. Mean mineral mass is mineral mass divided by bone width and is expressed in g/cm². The standard mineral mass (g/cm) was used to follow changes in mineral mass whereas the standard mean mineral mass (g/cm²) was used when comparisons were made between different groups of patients. Application of a standardized measuring procedure has resulted in a coefficient of variation of less than 2% for repeated measurements on consecutive days on the same individual (Linder  rd et al., 1974). A complete measurement on one patient is done in about 30 min and is totally harmless and easy to the patient. All calculations are made by computer with a minimum of time and cost.

In this study measurements have routinely been performed at two month intervals for as long as 24 months before the parathyroid exploration. One measurement was performed immediately before the operation and then measurements were done on the first and fifth day after the operation, the second and fourth week after, the second, third and sixth month after and then at two to four months interval up to 24 months postoperatively.

Hemodialysis treatments were performed twice weekly, 8–11 hours each, for institutional dialysis patients and three times weekly, 21–30 hours a week, for homedialysis patients. Gambro Lundia Nova dialysators with 13.5 μ membranes were used. The calcium content in dialysis fluid was kept constant at 3.5 mEq/l.

Serum calcium, serum phosphates and serum alkaline phosphatases were measured according to conventional laboratory methods.

All blood samples were drawn immediately before the start of hemodialysis and after the longer interval between two dialysis treatments.

Serum parathyroid hormone (s-PTH) was analysed by a radio-immuno-assay technique (Almqvist, Hj  rn & W  st  d, 1975).

Se⁷⁵-methionin scintigraphy of the parathyroids was performed according to Potchen, Adelstein & Dealy (1965) and Keeling & Todd-Pokropek (1969). Radiological examinations of the skeleton were performed by routine methods. The parts of bone examined were hands, forearms, shoulders, spine, pelvis, lower limbs and feet.

Total parathyroidectomy was done in nine patients and subtotal parathyroidectomy, leaving one half of a normal gland, in one (case 3). Microscopic examination of the excised glands was performed in all cases. The statistical analysis was performed with the use of regression analysis and the Student's *t*-test.

MATERIAL

All uremic patients with final renal insufficiency selected for parathyroidectomy during 1972 to 1974 were included in this study. Of the ten total operated patients, eight had been on a regular hemodialysis treatment (RDT) programme for 5 to 50 months with a mean of 33.9 months (Table I). One patient (case 7) was operated on within one month before she went into hemodialysis and one patient (case 3) was first on RDT and then had a functioning renal transplant for 23 months before the operation. All patients were women with a mean age of 44.5 years.

The underlying renal disease was chronic pyelonephritis in five patients, polycystic kidney disease in three, chronic glomerulonephritis in one and unclassified nephropathy in one patient.

In six patients the serum calcium was constantly elevated (normal values 4.3–5.1 mEq/l) and in four patients occasional elevations were observed. The phosphate level was kept at a level where the calcium phosphate product (mg%) was within 40 and 70 with the use of an oral aluminium hydroxide preparation.

Table I. *Clinical characteristics in ten patients with final renal insufficiency explored for hyperparathyroidism*

Patient	Age	Diagnosis	RDT ^a (mo.)	S-Calcium mEqv/l	Alkaline phosphatase	S-PTH	⁷⁵ Selenium- methionin scintigraphy	Bone symptoms
1	59	Polycystic kidney disease	41	5.5–6.2	↑	↑	(+)	Pain
2	29	Glomerulo- nephritis	5	5.8–6.3	Normal	Normal	–	Tenderness
3	53	Pyelonephritis	10	5.1–5.5	Normal	↑	+	–
4	36	Pyelonephritis	43	5.4–5.9	Normal	↑	+	Pain
5	30	Pyelonephritis	29	5.4–6.2	Normal	↑	–	Tenderness
6	55	Pyelonephritis	37	4.6–6.3	Normal	↑	+	Pain Tenderness
7	34	Pyelonephritis	0	5.4–5.9	Normal	↑	+	–
8	41	Polycystic kidney disease	23	4.5–5.3	↑	↑	+	Pain Tenderness
9	47	Unclassified nephropathy	50	4.8–6.8	↑	Normal	–	Pain Tenderness
10	61	Polycystic kidney disease	43	4.5–5.5	↑	↑	–	Pain

^a Regular dialysis treatment.

The alkaline phosphatases were normal in six patients. In three patients a continuous increase of the alkaline phosphatases were noted preoperatively. S-PTH was normal in two patients, moderately elevated in six patients and highly elevated in two patients (cases 8 and 10).

⁷⁵Seleniummethionin scintigraphy of the parathyroid glands were normal in four patients, positive for adenoma and/or hyperplasia in five patients and uncertain in one patient.

There were no clinical symptoms of bone demineralization in two patients. In eight patients symptoms such as bone tenderness and pain were reported and in one of these patients spontaneous fractures occurred. Routine radiological examination of the bone was normal in one patient (Table II). In three patients subcortical erosions consistent with osteitis fibrosa were found. In the remaining six patients, non-specific decalcification were noted.

Histological examination of the excised glands showed normal parathyroid tissue in one case (case 9) and adenomatous hyperplasia in the other nine patients.

Aluminium hydroxide was administered to eight patients pre- and postoperatively in about the same amount. Vitamin D₃ or dihydrotachysterol was usually not given before the operation because of the already elevated calcium levels but was tried for shorter periods in two patients.

Postoperatively, it was possible to administer dihydrotachysterol and/or calcium preparations to eight patients.

The amount of dihydrotachysterol and calcium preparations consumed per month decreased abruptly after the first month after the operation and then slowly.

Postoperatively, serum calcium was reduced to normal in all cases. In eight patients the serum calcium was subnormal for a short period of time postoperatively and then went back to normal.

Alkaline phosphatases were normalized in three of

those four patients who had elevated values before the operation.

Routine X-ray examinations postoperatively showed

Table II. *Pre-operative evaluation of bone mineral mass in ten patients with final renal insufficiency explored for hyperparathyroidism*

Patient	Bone densitometry, per cent decrease compared with normals ^a	Clinical radiology
1	6	Slight subcortical erosion
2	10	Normal
3	3	Moderate decalcifi- cation
4	26	Slight decalcifi- cation
5	8	Slight decalcifi- cation
6	1	Moderate decalcifi- cation
7	23	Slight subcortical erosions
8	31	Marked decalcifi- cation, slight subcortical erosion
9	32	Marked decalcifica- tion, spontaneous fractures
10	34	Marked decalcifica- tion

^a Normals matched for sex and age.

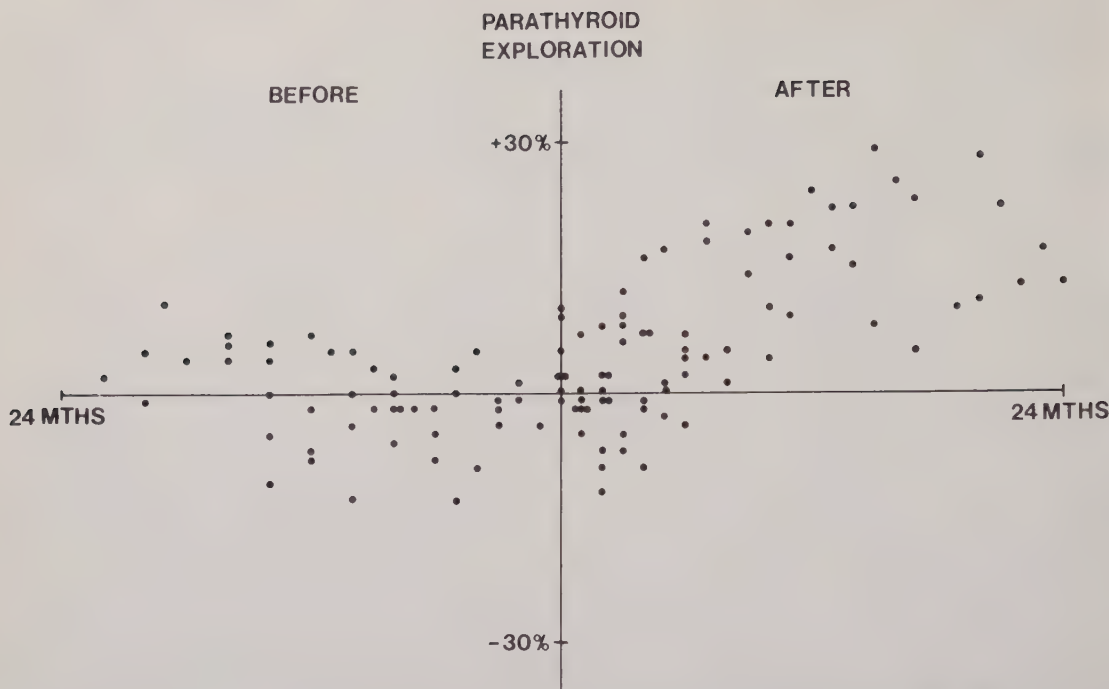


Fig. 2. Bone mineral mass (g/cm) expressed as per cent change from the mean of the pre-operative measurements

for each of ten patients with final renal insufficiency explored for hyperparathyroidism.

healing of subcortical erosions in one of two patients and healing of non-specific decalcifications were noted in three of seven patients.

RESULTS

The results of the measurements with bone densitometry before and after parathyroid exploration is presented in Fig. 2. The variations in bone mineral mass before operation showed no significant changes either in isolated cases or in the whole group of patients. Postoperatively, however, an increase in mineral mass was registered which became significant after 7 months ($p < 0.005$).

The increase was highly significant ($p < 0.001$) for the whole group of patients who were followed up to 24 months after the operation. Pre- and post-operative values on bone mineral mass (g/cm) for each separate patient are presented in Table III. In four out of ten patients a decrease in mineral mass beyond the error of the method was observed during the first months postoperatively. Thereafter an increase in mineral mass was noted in all cases and the increase was significant ($p < 0.005$) in five patients.

A comparison between sex- and age-matched controls, patients on regular hemodialysis treatment at our hospital and the parathyroidectomy patients using the standard mean mineral mass (g/cm²) is presented in Fig. 3. The mean mineral mass was significantly lower among the parathyroidectomy patients than among the non-operated patients on regular hemodialysis treatment ($p < 0.025$). Compared to the normals the mean mineral mass was considerably lower among the parathyroidectomy patients ($p < 0.001$).

After the parathyroid exploration improvement towards normal values was noticed also in the standard mean mineral mass (g/cm²) (Fig. 4).

CASE REPORT

A typical case report (no. 8) will be presented.

The patient is a 41-year-old house-wife with three children. Polycystic kidney disease complicated by hypertension was diagnosed in 1965. Because of progressive uremia, chronic hemodialysis was initiated in 1971. In 1972 she started to complain of itching, bone pain and tenderness and was therefore considered for parathyroidectomy. Bone radiology showed marked decalcification. Subcortical erosions in the distal phalanges of the

Table III. Bone mineral mass (g/cm) in distal forearm in ten patients with final renal insufficiency explored for hyperparathyroidism

Each value represents the mean for the period. Figures in parentheses indicate the number of measurements

Patient no.	Months before operation				Months after operation						
	24.0–18.1	18.0–12.1	12.0–6.1	6.0–0.0	0.0–1.0	1.1–2.0	2.1–3.0	3.1–6.0	6.1–12.0	12.1–18.0	18.1–24.0
1	–	–	2.66 (3)	2.61 (4)	–	2.61 (1)	–	2.63 (3)	2.88 (1)	3.01 (1)	–
2	–	–	–	3.37 (1)	–	3.43 (1)	–	3.55 (2)	3.51 (2)	3.58 (2)	3.81 (5)
3	–	–	–	2.31 (2)	–	2.50 (1)	2.50 (1)	2.47 (1)	2.34 (1)	–	–
4	2.50 (1)	2.21 (2)	2.01 (1)	2.32 (2)	2.24 (4)	2.30 (1)	2.46 (1)	–	2.68 (3)	2.77 (2)	–
5	2.65 (1)	2.69 (2)	2.69 (4)	2.67 (4)	2.63 (2)	2.44 (1)	2.54 (1)	2.60 (1)	–	–	–
6	–	3.36 (1)	3.27 (3)	3.19 (4)	3.46 (3)	3.24 (1)	–	3.22 (3)	3.52 (1)	–	–
7	–	–	–	3.03 (1)	2.98 (5)	3.01 (2)	–	3.22 (2)	3.64 (1)	3.72 (2)	3.70 (1)
8	–	2.86 (1)	2.54 (7)	2.79 (2)	2.69 (3)	2.37 (2)	3.01 (2)	3.13 (3)	3.26 (3)	3.33 (2)	3.46 (1)
9	–	–	–	1.95 (2)	1.91 (4)	–	2.06 (1)	–	2.17 (3)	–	–
10	2.10 (4)	2.08 (3)	1.96 (3)	1.88 (2)	1.93 (3)	1.89 (1)	1.89 (1)	1.91 (2)	–	–	–

hands were present. S-Ca was elevated to 5.3 mEq/l (normal 4.3–5.1). The alkaline phosphatase levels were steadily increasing during the year before the operation from 10 to 40 Bodanski units. S-PTH was >20 ng/ml. ⁷⁵Selenium-methionin scintigraphy revealed an increased uptake corresponding to the lower right and upper left

parathyroid gland. At the neck exploration, a marked hyperplasia of all four glands was noted. A total parathyroidectomy was performed. The removed parathyroid tissue weighed 16 g. Histological examination of the excised glands showed adenomatous hyperplasia.

Postoperatively s-Ca fell to 3.3 mEq/l. S-Ca remained

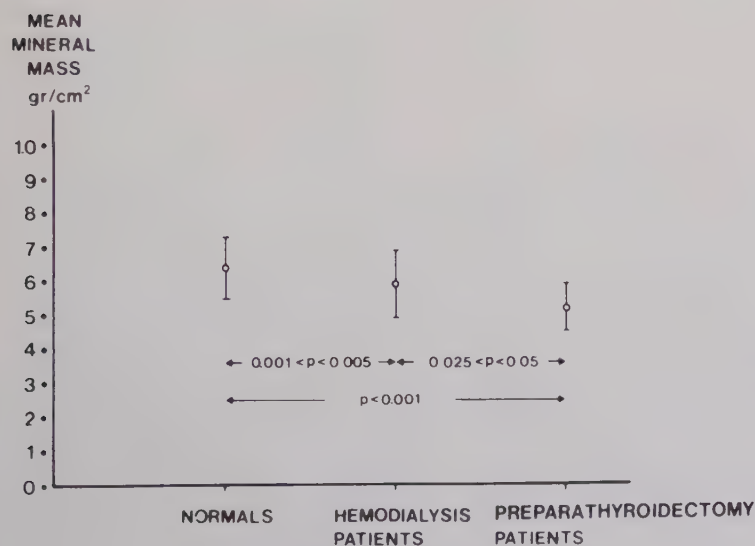


Fig. 3. Mean mineral mass (g/cm²) expressed as mean $\pm$ 1 S.D. in normals, a group of regular hemodialysis patients and pre-operatively in ten patients with final renal insufficiency explored for hyperparathyroidism.

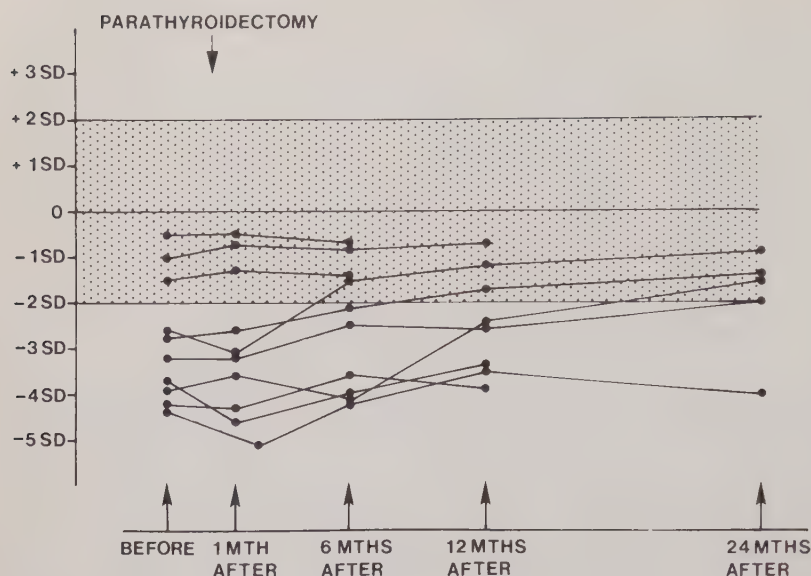


Fig. 4. Mean mineral mass (g/cm^2) before and after parathyroidectomy in a group of patients with final renal insufficiency. The value of mean mineral mass for each patient is presented in standard deviations (S.D.) from a sex- and age-matched normal material.

low for two months in spite of heavy treatment with calcium gluconate and dihydrotachysterol. S-alkaline phosphatases dropped to nine Bodanski units postoperatively and has since remained within the normal range. Postoperatively the patient was transferred from institutional hemodialysis to homedialysis training and three months later she was dialysing herself at home. Bone radiology after 12 months showed increased mineralization and disappearance of the subcortical erosions.

Fig. 5 indicates the changes in bone mineral mass pre- and postoperatively. Pre-operatively, the mean value of mean mineral mass (g/cm^2) was 31% below normal females. Compared to the mean values for the patients undergoing chronic hemodialysis, the reduction in bone density was 27%. During the first two months postoperatively, a marked reduction of bone density occurred. Thereafter, there was a continuous increase in bone mineral.

DISCUSSION

Reactive hyperparathyroidism is a common complication in uremic patients treated with regular hemodialysis. The criteria used in selecting patients for parathyroid exploration are often based on subjective signs such as itching and bone pain or tenderness. The renal osteodystrophy has a central position in the pre-operative evaluation of the patient. Laboratory findings does not provide reliable information about the degree of renal osteodystrophy.

There is a significant clinical need for methods reflecting the grade of bone mineralization. This is desirable both for pre-operative evaluation and as means for following the effect of the parathyroid

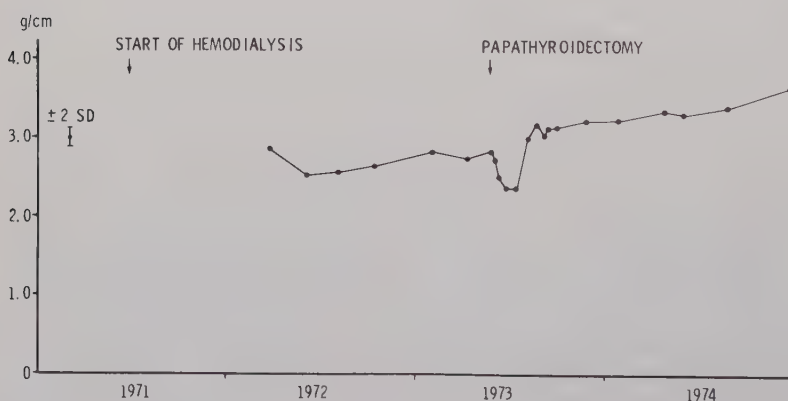


Fig. 5. Bone mineral mass (g/cm) in one patient on regular hemodialysis explored for hyperparathyroidism (case 8). The variation of the method is indicated with ± 2 S.D.

surgery. In previous studies, bone densitometry has been shown to be a valuable technique for assessing bone mineral mass. The advantages with this method are that it can be repeated as often as needed and is completely harmless to the patient. In previous studies, the reproducibility of the method has been shown to be good. With proper data processing procedures, the result of the recordings can be achieved momentarily. The limitations of the method is that it only provides the total mineral mass and hence does not give information about the quality of the demineralization. Also the measurements are confined to one certain spot of the bone system viz. the midshaft of the radius and ulna, which by some authors are considered less sensitive for variations in the mineralization (Dalén & Jacobsson, 1974). Alternative methods which can be used are diagnostic radiology and bone biopsy.

The limitation of the diagnostic bone radiology is its reduced sensitivity to dynamic changes in the mineralization state. Bone radiology is also difficult to quantitate. The advantages with X-ray of the bone is that it provides a morphological picture of the mineralization process. The biopsy approach has a limited value because it cannot be repeated as often as wanted. The morphological information provided by this method, however, is far superior to those previously mentioned.

The patients included in this study have been selected from one dialysis centre and they have been selected for operation consecutively. The total dominance of women in this material is difficult to explain. There was an equal sex distribution in the total group from which the patients were selected. The diagnosis of reactive hyperparathyroidism was based upon several subjective and objective criteria. Most patients demonstrated various forms of subjective signs, most commonly itching and bone tenderness. The laboratory findings were more varied but some elevation of the s-Ca level was found, preoperatively, in all patients. Half of the patients had a maximal s-Ca level elevation below 6 mEq/l. Serum alkaline phosphatases were elevated in four patients. After the removal of the parathyroid glands only one patient had constantly elevated values. In the other three patients serum alkaline phosphatases were normalized. The clinical validity of s-PTH is doubtful in uremic patients because of difficulties in identifying the pertinent PTH-fraction and the skeletal resistance to PTH. In

the present material eight patients showed elevated levels of PTH, in some cases considerably elevated. One patient with normal PTH level (case 9) had normal glands on histological examination.

Vitamin D treatment was instituted in two patients pre-operatively. Both of these patients had severe renal osteodystrophy.

Postoperatively, most of the patients were given considerable amounts of vitamin D preparations and calcium.

Calcium infusions were often required in the immediate postoperative course. Large doses of vitamin D and calcium were well tolerated during the first postoperative months and the amount of vitamin D and calcium was increased to highest possible level in order to accelerate the mineralization process. In the later course, the vitamin D and calcium were less well tolerated and reduction of doses were necessary.

The mean mineral mass (g/cm^2), pre-operatively, was markedly reduced compared to a group of normal females. Even in comparison with the total group of patients undergoing hemodialysis, there was a statistically significant reduction. Bone densitometry can not be used as the sole discriminant factor in selecting patients for operation but can be of value when used together with other parameters. The pre-operative level of mineral mass varied in each individual case but the values for each patient and for the total group did not disclose any systematic changes. Thus, it seems that the mineralization status of the patients, was stable up to the time of operation. The dynamic changes occurring in bone mineral mass, postoperatively, were easily recognised by the method. Statistically significant increases in bone mineral mass were present in five individuals after ten months and were also found for the whole group of patients taken together after seven months. In some of the patients, significant increases could be recorded earlier. From these observations, it is obvious that marked changes in bone mineral mass can be recorded in the distal shaft of the radius and ulna.

During the first months, postoperatively, four of the patients demonstrated a reduction of the bone mineral beyond the error of the method. In one patient (case 8), there was a 25% loss of mineral mass in distal forearms within two months postoperatively. To our knowledge, such a dramatic postoperative decrease has not been observed before although it has been hinted by some authors

(Hosking, Chamberlain & Fremlin, 1972; Dalén & Hjern, 1974).

It is known that PTH increases bone resorption and hence the mobilization of calcium out of the skeleton (Rasmussen, Bordier, Kurokawa, Nagata & Ogata, 1974; DeLuca, 1975). When the PTH secretion is suddenly stopped after a parathyroidectomy it can be expected that the calcium content in the bone again will increase in parallel with a decrease in s-Ca.

Usually s-Ca falls postoperatively both after partial and total parathyroidectomy (Stanbury et al., 1960; Ogg, 1967). It has also been suggested that a deposition in bone of calcium carbonate (Stanbury et al., 1960) or phosphate with calcium (Ogg, 1967) could explain this fall in s-Ca. In our study, however, a more or less severe decrease in s-Ca was noted and in four cases there was a transient, simultaneous decrease in bone mineral content. Thus, the decrease in s-Ca can not be explained by interruption of a PTH-dependent demineralization, at least not from the cortical bone in forearms where our measurements have been performed. It cannot be excluded that increased mineralization has occurred in other parts of the skeleton but bone mineral content in cortical bone in forearms evaluated by photon absorption technique has been reported to correlate well with mineral content in other parts of bone as well as in total bone (Mazess, 1971; Chestnut, Manske, Baylink & Nelp, 1973). Other possible losses of s-Ca are deposits outside bone, fecal losses and renal losses. No noticeable soft tissue calcifications have been observed on routine X-ray examinations and the urine production is negligible in our patients. It should be pointed out that total parathyroidectomy has been done in these four cases and the postoperative hypoparathyroidism is then absolute. As it is known that PTH stimulates the synthesis of $1.25(\text{OH})_2\text{D}_3$ (DeLuca, 1975), the last step in the metabolism of vitamin D, it might be possible that there is a temporary loss of calcium via faeces. No patients demonstrating the same type of postoperative reduction were immobilized more than the other patients who all passed an ordinary postoperative program with early ambulation. The size of the surgical trauma was also equal in all cases in this study.

The present investigation indicates that bone densitometry provides valuable information on the bone mineral status of uremic patients who are candidates for parathyroidectomy. The difference

from other patients treated with chronic hemodialysis is, however, not great enough to warrant the use of bone densitometry as the only discriminating instrument. Bone densitometry is of greater interest in following the effect of parathyroidectomy on bone mineralization. Most of our patients showed an increase in the mineral content after parathyroidectomy, in some cases after an initial decrease. Although measurements have been performed only on the distal shafts of both forearms, i.e. on cortical bone, significant changes have been noted.

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..... the stone was uneven and broken, and the letters were straggling and irregular, but (Dickens 1836).

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Bone Morphologic Parameters of Renal Osteodystrophy
in patients on Regular Hemodialysis.

Short Title: Bone Morphology in Regular Hemodialysis.

O. Johnell, B. Lindergård, B.E. Nilsson and P.E. Wiklund

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Summary

Parameters of renal osteodystrophy such as abundance of osteoid, osteoclast activity, and abundance of calcification fronts were studied in 72 patients on maintenance hemodialysis, and compared with laboratory and clinical data. It was found that parathyroid hormone activity and alkaline phosphatase had some relevance in the prediction of bone changes but such changes were difficult to predict in the individual case. Laboratory variables were also difficult to use for differing between the two main types of changes - secondary hyperparathyroidism and osteomalacia. A difference was found between cases of glomerulonephritis and cases with polycystic kidney disease or pyelonephritis in that the two latter groups had more than double the amount of osteoid in their biopsies than had the glomerulonephritis cases. Patients without kidneys did not, however, deviate from the remainder in their degree of osteomalacia. The abundance of osteoclasts in the biopsy may be a predictor of a future development of hypercalcemia leading to parathyroidectomy.

Key words: Hemodialysis, sec. hyperparathyroidism, osteoclasts, osteomalacia, alkaline phosphatase.

Skeletal complications to regular hemodialysis and/or chronic renal failure were already presented in the early era of hemodialysis (1). Since then a considerable number of investigators have provided evidence for this fact. One skeletal consequence of hemodialysis is a reduction of the bone mineral mass (2, 3). Systematic bone biopsy studies on the frequency and quantity of the morphologic changes have been presented by Bishop et al. (4), Bordier and Tun Chot (5), Duursma et al. (6) and others.

Hruska et al. (1978) (7) subdivided a series of patients undergoing hemodialysis with regard to the bone morphology in secondary hyperparathyroidism, osteomalacia and mixed cases and suggested from their findings that biopsy is a necessity for the assessment of uremia-related bone disease.

The aim of our study was to quantitate morphological changes in a series of hemodialysis patients and to relate these quantities to clinical and laboratory findings.

Material and Methods

Included in the study were 72 patients undergoing maintenance hemodialysis. There were 36 women with a mean age of 43 (range 18-60) and 36 men with the same mean age of 43 (range 21-67). The duration of hemodialysis was on average 21 months (range 1-95). The renal diseases which had caused the uremia were glomerulonephritis (21 patients), pyelonephritis (24 patients) and polycystic kidney disease (9 patients), the remainder (18 patients) being a variety of renal disorders.

Dialysis treatment was performed twice weekly, 8-11 hours each time in those patients who were given hemodialysis in hospital and three times weekly, altogether 15-30 hours per week, for home hemodialysis patients. The Alwall-Gambro and the Gambro-Lundia and a few other disposable parallel flow dialysers, 1.0-1.8 m², were used. The calcium content in the dialysis fluid was 1.75 mmol/l and the calcium-phosphate product was kept at 3.3-5.6 mmol.

Four patients, however, on hemodialysis for more than 4 years, had initially been treated with the Alwall cylinder dialyser model 1952 with a priming volume of 1200 ml. Furthermore, the 14 earliest patients included in this series had been subjected to dialysis fluid with a calcium concentration of 1.5 mmol/l.

In all patients an iliac crest biopsy was performed. A 5 x 15 mm bone cylinder was removed from the iliac crest by a slow moving motor-driven miller. The sample was embedded in methyl-metacrylate and sectioned undecalcified. A point-wave template (8) and a ruler, both engraved in the eye-piece of the microscope, were used for the morphometric evaluations. Only trabecular bone was evaluated. The sections were stained according to Goldner (9) and the following variables measured:

Trabecular volume (per cent of total bone tissue volume).

Osteoid surface (per cent of trabecular surface).

Osteoclast activity (number of osteoclasts per mm² of total surface (10)).

The samples of those patients who had more than 5 % osteoid in the evaluation of the Goldners stained sections were also sectioned and stained with toluidine blue and studied for calcification fronts (Figure 1).

Parathyroid hormone (PTH) was measured by an immuno-assay method within 6 months of the biopsy (11).

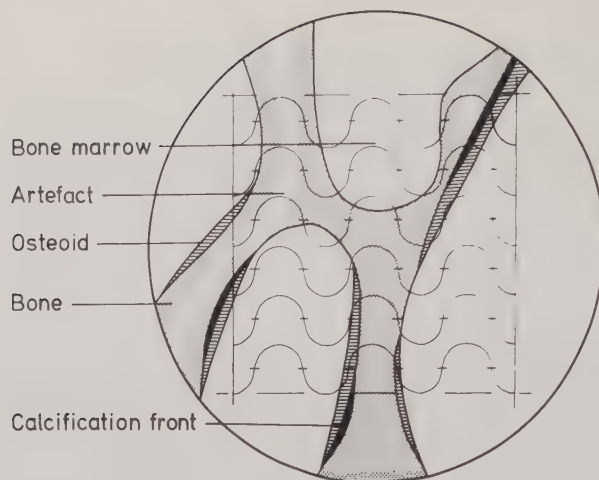


Figure 1. Schematic representation of morphometric variables in a trabecular bone sample.

The bone mineral content (BMC) of the forearms was measured by the method of gamma-absorptiometry (Gambro Bone Mineral Detector) and calculated as the average thickness (g/cm^2) of bone mineral in the pathway of a beam scanning across the radius and ulna shafts (12). The measurements were compared with data obtained from 136 healthy subjects (without known bone lesions) (13). In addition, serum calcium (S-Ca), serum phosphate (S-PO_4), serum alkaline phosphatase (S-Alk.ph.) were measured simultaneously with the biopsy.

Four groups were constituted, based on the morphologic findings:

No bone disease = less than 0.12 osteoclasts/ mm^2 of bone, less than 12 % osteoid surface.

Secondary hyperparathyroidism = osteoclast activity exceeding 0.12 cells/ mm^2 , osteoid surface less than 12 %.

Osteomalacia = osteoclast activity less than 0.12 cells/ mm^2 , osteoid surface exceeding 12 %.

Combined bone disease = osteoclast activity exceeding 0.12 cells/ mm^2 and osteoid surface exceeding 12 %.

The limits were obtained from previous studies of normal cases (10, 14).

Two special groups could be distinguished which with regard to their clinical course differed from the main group:

1. Six anephric patients, who had undergone bilateral nephrectomy 2.8 ± 1.7 years prior to the biopsy.
2. Thirteen patients in whom parathyroidectomy was performed 4.0 ± 1.8 years after the biopsy. The decision to operate was taken because of hypercalcemia. The osteoclast count was not known by the clinicians at the time of the operation.

Three of the patients belonged to both groups.

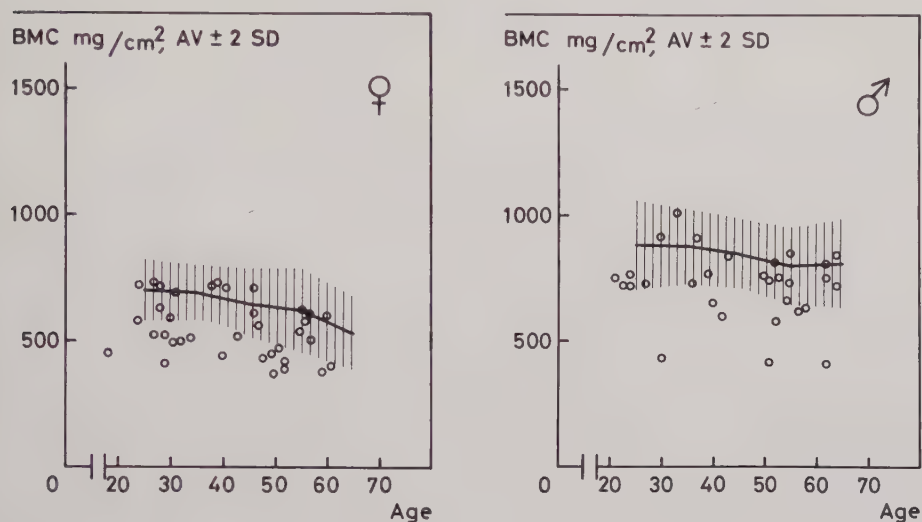


Figure 2. Bone mineral content in patients undergoing hemodialysis. A. Women, B. Men. Shaded areas represent two standard deviations in healthy individuals.

Results

Since there were no differences between the sexes, except for the measure of BMC, the data have been pooled. The BMC was significantly ($p < 0.001$) lower in both sexes than in the healthy subjects (Figure 2). The distribution of osteoclast counts and osteoid is presented in Figures 3 and 4. In the hemodialysis patients there was a considerable scatter in the measurements from normal to highly pathological values.

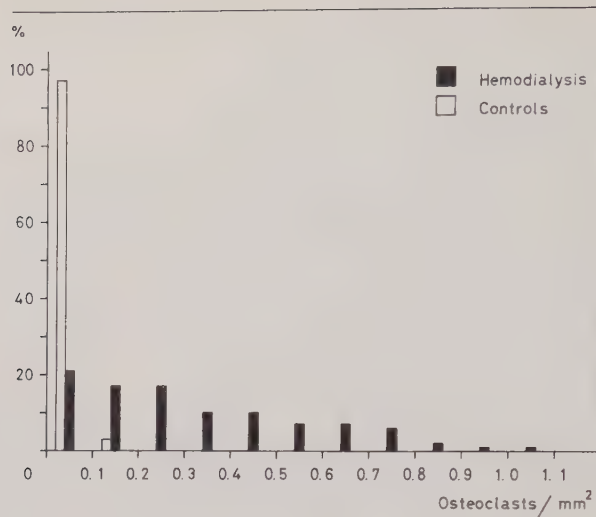


Figure 3. The distribution of osteoclast counts in hemodialysis patients as compared with healthy individuals.

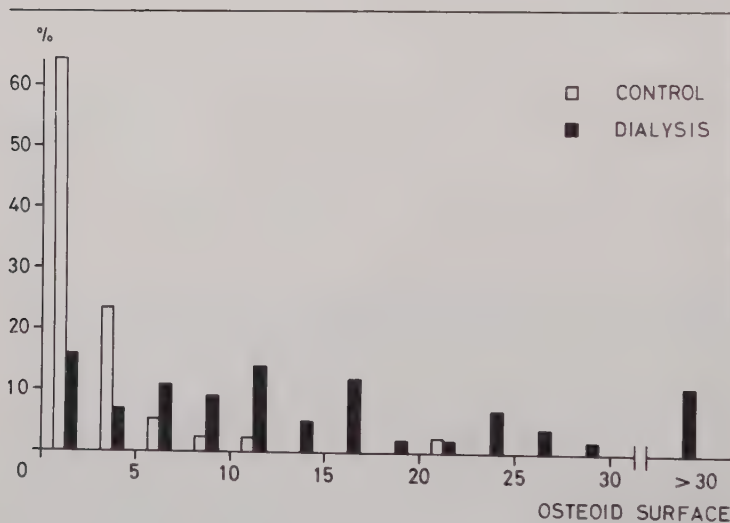


Figure 4. Distribution of osteoid surface in hemodialysis patients as compared with healthy individuals.

The relationship of calcification fronts (active osteoid) and total osteoid surface is shown in Fig. 5. For patients with osteoid exceeding 5 % the values of calcification fronts were decreased to about 1/3 of normal values. In Table 1 the morphometric and laboratory variables have been presented in a correlation matrix. A potential to predict a high osteoclast activity was found for the PTH-values, the $S-PO_4$ values and S-Alk.ph. A long duration of hemodialysis was also related to a high osteoclast count. Except for a tendency of increasing osteoid with age none of the variables measured in this study had any potential to predict the amount of osteoid in the trabecular bone. The duration of hemodialysis appears to be related to most of the negative effects measured in this study, but the levels of significance were low in most instances.

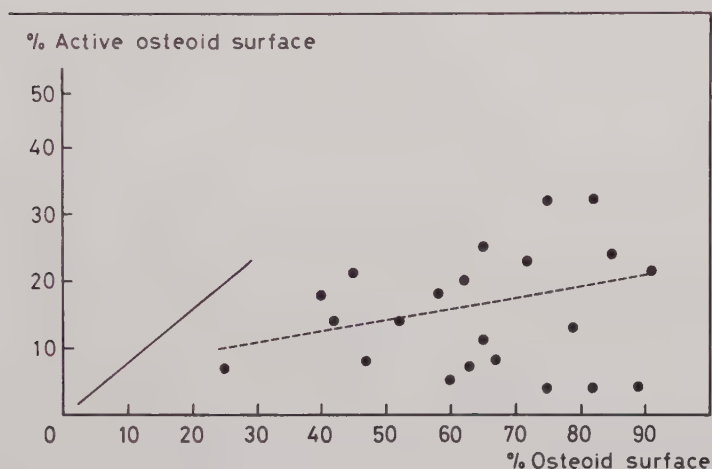


Figure 5. The relationship of calcification fronts and total osteoid surface in hemodialysis patient (-----). The regression line of the same variables in normal controls (——) is included.

Our attempt to subdivide the patients into four groups: no bone disease, secondary hyperparathyroidism, osteomalacia, and combination of the two is presented in Table 2 together with the quantities of the various parameters of bone disease. Similar tendencies are seen. Note that renal osteomalacia with increased osteoid surface but without increased osteoclast activity was found in only three cases. However, this group, because

Table 1. Positive (pos) or negative (neg) slope or no trend (-) and probability levels of linear correlation (n.s. = insignificant, (*) = 0.1 > p > 0.05, * = 0.05 > p > 0.02, ** = 0.02 > p > 0.01, *** = 0.01 > p > 0.001, **** = p < 0.001).

	Age	Osteo- clasts	Bone volume	Osteoid surface	Bone mineral content	PTH	S-PO ₄	S-Ca	S-alk. phosph.
Osteoclasts	neg *								
Trabecular volume	neg (*)	pos (*)							
Osteoid surface	pos *	- n.s.	pos n.s.						
Bone mineral content	neg n.s.	neg n.s.	pos n.s.	neg n.s.					
PTH	neg n.s.	pos ***	pos n.s.	neg n.s.	pos n.s.				
S-PO ₄	neg n.s.	pos **	pos n.s.	neg (*)	pos (*)	pos **			
S-Ca	pos n.s.	pos n.s.	neg n.s.	neg n.s.	neg n.s.	neg *	pos n.s.		
S-alk. phosph.	neg n.s.	pos ****	pos n.s.	pos n.s.	neg n.s.	neg n.s.	pos n.s.		
Duration of hemodialysis	neg n.s.	pos ***	pos n.s.	pos n.s.	neg (*)	pos n.s.	pos n.s.	pos n.s.	pos ****

of the small number and the scatter of the data cannot be distinguished from the others, nor is it possible to separate the hyperparathyroid cases from those combined with osteomalacia. A comparison between the three main diagnostic groups revealed that both pyelonephritis and polycystic kidney disease had significantly higher osteoid values, i.e. osteomalacia, than glomerulonephritis cases. $S-PO_4$ was also decreased, significantly only in pyelonephritis.

The anephric patients had an increased osteoid content and PTH activity but the increases were not significant (Table 3). The patients who were going to be parathyroidectomized in coming years had an almost doubled osteoclast count and an insignificant increase in PTH (Table 3).

Discussion

The symptoms due to uremia per se tend to conceal the skeletal consequences. It would therefore be of value to find a simple non-invasive method to detect early bone changes. It has been demonstrated that prospective intermittent measurements of bone mineral is a sensitive method in hemodialysis cases (15, 16). However, such a method does not distinguish between the main types of renal osteodystrophy. Bone mineral measurement using gamma-absorptiometry in the present study, combined with laboratory tests and clinical information, was found to have a low ability to predict the morphologic changes in the bone as measured by the osteoclast activity and the abundance of osteoid. The serum phosphate and the serum calcium are of little value since these parameters are affected by the hemodialysis procedure itself, whereas the alkaline phosphatase has some potential to predict morphologic changes but not the type of change. Furthermore, the scatter of these variables decreases their usefulness. Therefore, it must be concluded that, today, we cannot avoid a bone biopsy if we want a differential diagnosis in patients with suspected renal osteodystrophy.

In the present study pyelonephritis and polycystic kidney disease are associated with a higher amount of osteoid as compared with glomerulonephritis. This difference may be caused by a difference in the ability of the diseased kidneys to perform the final steps in the vitamin D-hydroxylation. On the other hand, the six patients without kidneys did not deviate in their degree of osteomalacia, in spite of the fact that such patients are unable to produce detectable amounts of 1.25-dihydroxycholecalciferol (17). A similar lack of impact on the bone histology after bilateral nephrectomy was demonstrated by Bordier et al. (18) who concluded

Table 2. Variables in hemodialysis patients, quantities and comparisons between groups (probability levels as in Table 1).

	Number of patients	Average	SD	Normal range	Sec. hyperparathy. (n=27)	Osteomalacia (n=3)	Combined bone disease (n=22)	Deviation (%) from patients with no bone disease (n=14):	Deviation (%) from patients with chronic glomerulonephritis (n=21):	Polycystic kidney disease (n=9)
Age, years	72	43	13		-1 n.s.	+19 n.s.	+5 n.s.		+14 n.s.	+36***
Osteoclasts number/mm ²	72	0.32	0.26	<0.12	-	-	-		+6 n.s.	+6 n.s.
Trabecular volume, %	71	19	6	-	+18 n.s.	-3 n.s.	+13 n.s.		-1 n.s.	+34**
Osteoid surface, %	71	15	16	<12	-	-	-		+145*	+157*
BMC, g/cm ²	64	0.62	0.17	-	-6 n.s.	0 n.s.	-12 n.s.		-6 n.s.	-2 n.s.
PTH, ng/ml	45	8.0	7.9	1.1-2.5	+180*	+110**	+170*		-23 n.s.	-3 n.s.
PO ₄ , mmol/l	69	1.9	0.5	0.7-1.6	+31*	+23 n.s.	+13 n.s.		-21 n.s.	-18 n.s.
Ca, mmol/l	69	2.4	0.3	2.2-2.6	+4 n.s.	+6 n.s.	0 n.s.		+3 n.s.	-3 n.s.
Alk. phosph., units/l	68	236	161	50-275	+54*	+32 n.s.	+76*		-16 n.s.	-4 n.s.
Duration, months	69	21	19		+68 n.s.	+15 n.s.	+29 n.s.		-14 n.s.	-42 n.s.

that normal bone mineralization may take place in the absence of kidneys. The same authors found, as in the present study, an increased tendency of secondary hyperparathyroidism in anephric patients.

Finally, our data suggest that a future development of secondary hyperparathyroidism and the subsequent need for parathyroidectomy may be predicted from an iliac crest biopsy with osteoclast count.

Table 3. Anephric patients and patients who went on to parathyroidectomy compared with other dialysis patients.

	Anephric		Others		Diff. %	Later PTX		Others		Diff. %
	N	Mean SD	N	Mean SD		N	Mean SD	N	Mean SD	
Osteoclast number/mm ²	6	0.47 [±] 0.38	66	0.31 [±] 0.24	+ 52 (n.s.)	13	0.53 [±] 0.32	59	0.28 [±] 0.21	+ 84 (p < 0.001)
Osteoid surface %	6	16 [±] 10	65	15 [±] 18	+ 7 (n.s.)	13	11 [±] 9	58	16 [±] 19	- 31 (n.s.)
PTH ng/ml	5	8.1 [±] 8.2	40	6.6 [±] 3.3	+ 23 (n.s.)	11	11.7 [±] 7.3	34	6.7 [±] 7.7	+ 75 (p < 0.1)

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Renal osteodystrophy in patients dialyzed
for 10 years or more.

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Abstract

Renal osteodystrophy in patients dialyzed for 10 years or more.

Ten patients have been on regular hemodialysis for 10 to 16 years. Two of these belong to the small group that has been on uninterrupted hemodialysis for the largest number of years in Europe. The age was 13 to 59 years at the start.

The bone disease was studied with X-rays, bone densitometry, bone biopsy and routine laboratory tests. Five of the ten patients showed radiologically continuous increase in the sum of pathological findings. The other five showed at least a temporary decrease, mainly of subperiosteal erosions. Metastatic calcifications were noted in most patients, especially after treatment with potent vitamin D analogues. Bone densitometry showed low mineral content in most patients. Bone biopsy showed intense osteoclast activity.

Parathyroidectomy, if done early in the dialysis course, was the only treatment after which improvement could be seen.

In conclusion, the development of bone disease in patients on regular hemodialysis treatment is slow and seems to have been halted only during the last years.

Key words: Hemodialysis, Renal osteodystrophy, Densitometry, Bone biopsy, Parathyroidectomy.

Bone disease has proved to be one of the main problems in patients on regular hemodialysis treatment (RDT). Better means for prevention and treatment are still necessary despite improved calcium balance, increased calcium content in the dialysis fluid, phosphate regulation, early total or subtotal parathyroidectomy, modern vitamin D analogues, calcitonin and probably also despite good water preparation with elimination of aluminium.

In many cases the evolution seems to be slow but continuous as was pointed out by us in 1978 (1,2).

The intention of this study was to follow more in detail the development of renal osteodystrophy in patients followed for at least 10 years on RDT.

Patient material and management.

Treatment with RDT at our unit started in 1960 (3) and the patients who have been in the program for the largest number of years were started in 1964.

In 1964 the Alwall cylinder dialyser model 1952 with a priming blood volume of 1200 ml was used. Thereafter, different models of disposable parallel flow Alwall-Gambro, Gambro dialysers, and Gambro capillary dialysers have been used.

The calcium content in the dialysis fluid was variable until 1968, 1.5 mmol/l from 1968 and 1.7 mmol/l from 1972. The aluminium content in the water has only been measured during the last three years and has then been below 0.03 mg/l.

The calcium phosphate product (mmol) was kept between 3.2 and 5.6 by adding aluminium hydroxide preparations.

Table I shows some of the characteristics of the 10 patients who have been followed for 10 years or more. One patient (ML) received a kidney transplant twice, the first she kept for 10 months, the second for 12 months. Another patient (KO) had a kidney transplant for 2 months. The other patients were never exposed to a kidney transplantation. Two patients are on antiepileptic drugs (phenytoin and phenobarbital) for the last 10-11 years (SJ and BP). Two patients were splenectomized because of hypersplenism. One patient (BP) has signs of rheumatoid arthritis.

One patient is dead (EG), one is disabled by chronic leg ulcers and a lower leg amputation (SIA), one is retired but otherwise in good condition (SA). The other patients are working part-time or more.

Table 1. Patients followed for 10 years or more on RDT.

Patient	Sex	First dialysis start	Age of start	Diagnosis(a)	Bilateral nephrectomy (b)	Transplantation(b)	Parathyroidectomy (b)	Other operation(b)	Present status(c)
1. IO	F	1964	20	PN	-	-	1976	-	ID
2. SJ	F	1964	22	GLN	-	-	1978	-	HD
3. BP	F	1968	15	PN	1968	-	1975	Splenectomy, 1973 Hip replacement, 1975	HD
4. SIA	M	1968	27	GLN	1968	-	1975	Leg amputation, 1980	HD
5. EG	M	1968	59	CYST	-	-	-	-	Dead
6. ML	F	1968	13	PN	1969	1971, 1978	1977	Splenectomy, 1974	ID
7. KO	M	1969	34	GLN	-	1972	1976	-	HD
8. ELH	F	1970	33	PN	-	-	1973	-	HD
9. SA	F	1970	56	CYST	-	-	1973	-	ID
10. IJ	F	1970	31	NSCL	-	-	-	-	HD

a) Glomerulonephritis (GLN), Polycystic kidneys (CYST), Pyelonephritis (PN), Nephrosclerosis (NSCL)

b) Year of operation

c) Home hemodialysis (HD), Institutional hemodialysis (ID)

Methods

X-ray studies of the skeleton were performed regularly since the start of RDT and comprised at least both hands. In this study, however, only the results of the hand X-rays were analyzed. Plain film technique was used and during the last three years mammography technique. All the films were evaluated by two of us (SS and BL). The findings were categorized in: general and cystic decalcifications, soft tissue and small vessel calcifications, subperiosteal and ungual tuft resorptions.

All findings were graded from 0 to 3, and thus the maximum points for both hands were 12 for decalcification, metastatic calcification and resorption respectively and 36 points all together. Cortical thickness was measured according to Barnett and Nordin (4) on the middle of both os metacarpale II with the use of a magnification glass and expressed in per cent of the total bone width.

The bone mineral content was measured by a photon absorption technique as first described by Cameron and Sorenson (5) and later modified by us (6, 7). Measurements were made on the midshafts of both fore-arms. In the follow-up study the standard bone mineral content (BMC) expressed in g/cm was used, and when comparison with normal was made, the standard BMC/W (BMC divided by bone width) expressed in g/cm^2 was used. Correction of BMC/W for fat tissue was made with regard to the size of a fat hump laterally to the radius bone in the photon absorption profile (8).

A 5 x 15 mm cylindric bone biopsy was taken from the iliac crest according to Burkhardt (9). The sample was embedded in methyl-metacrylate and sectioned undecalcified into 5 μ thick specimens and stained according to Goldner (10). The trabecular bone was evaluated with regard to:

Bone volume (per cent of total bone tissue volume), osteoid surface (per cent trabecular surface covered by osteoid) and osteoclast activity (number of osteoclasts per mm^2 of total surface), (11, 12).

Serum parathyroid hormone (PTH) was analyzed by a radio-immuno-assay technique (13). S-calcium, S-phosphate and S-alkaline phosphatase were measured according to conventional laboratory methods.

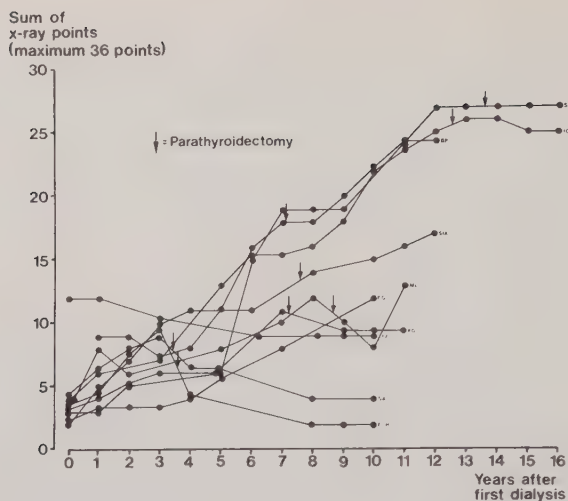


Figure 1. The point sum of the radiological findings = the course in 10 patients dialyzed for 10 years or more. Maximum 36 points. ↓ denotes parathyroidectomy.

Results

The point sum of the radiological findings is shown in Fig. 1. Already at the start of RDT all patients had some of the studied findings. In five patients there was a steady increase, in the other five there was at least a temporary decrease in the sum of findings. In four of the five patients this decrease ensued after a successful parathyroidectomy (PTX) but in one patient (IJ) a similar decrease was noted without PTX. The decrease was mainly due to a decrease in the subperiosteal and ungual tuft resorption (Fig. 2). Four patients showed either no change or a progression in bone resorption after PTX as illustrated in Fig. 3. Only one patient (EG) never showed signs of bone resorption. Metastatic calcification (Fig. 4) were noted in all but one patient and appeared late and in three cases after PTX with subsequent substitution of calcium and vitamin D preparations. Metastatic calcifications appeared or deteriorated in three of five patients after administration of $1-\alpha-D_3$.

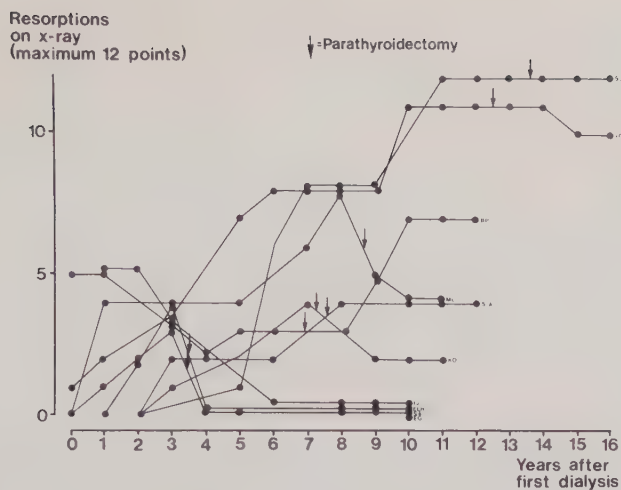


Figure 2. The course of resorption on X-ray in 10 patients dialyzed for 10 years or more. Maximum 12 points. ↓ denotes parathyroidectomy.

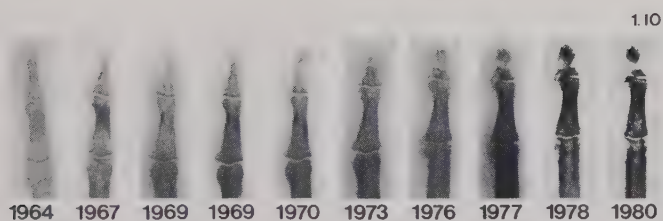


Figure 3. The radiological findings in the right index finger of one patient (I0) followed for 16 years on regular dialysis treatment (RDT).

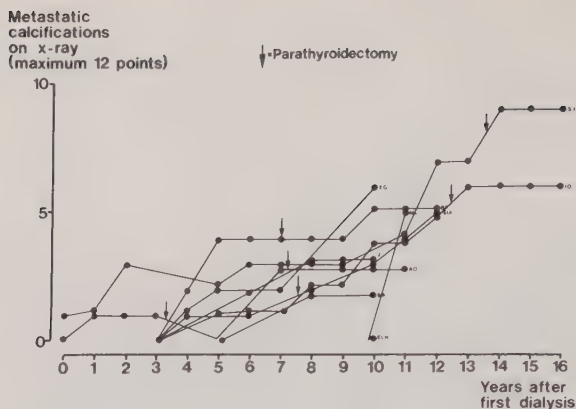


Figure 4. The course of metastatic calcifications on X-ray in 10 patients dialyzed for 10 years or more. Maximum 12 points.
↓ denotes parathyroidectomy.

The cortical thickness significantly decreased in all but two patients showing straight lines with a slope of from 0.03 to 0.13 % per month (Fig. 5). One patient (BP) developed bilateral osteonecrosis of caput femoris and was operated with total arthroplasty.

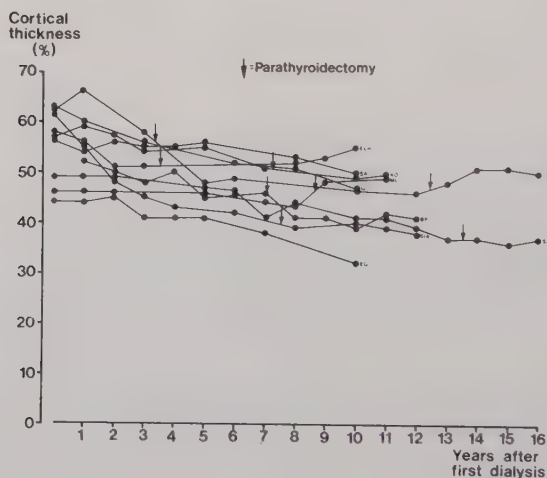


Figure 5. The change of cortical thickness on X-ray in 10 patients dialyzed for 10 years or more. ↓ denotes parathyroidectomy.

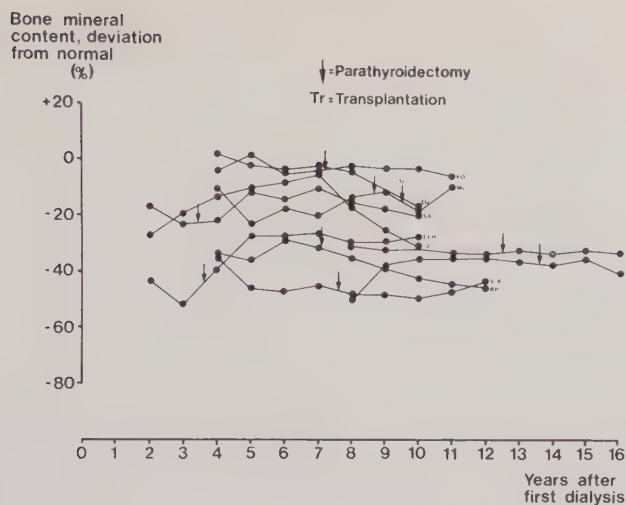


Figure 6. Bone mineral content in 10 patients dialyzed for 10 years or more. For details see text. ↓ denotes parathyroidectomy. Tr denotes kidney transplantation.

The mineral content was followed with bone densitometry since 1972 (Fig. 6). The curves were adjusted to the per cent deviation of BMC/W (g/cm^2) from normal at 10 years on RDT. The change from this time was expressed in per cent of the measured BMC (g/cm). After 10 years on RDT four patients had values within 2 SD-s of normal, the other patients were abnormal down to -6.2 SD-s from normal. In the patients who had been in the dialysis program for the largest number of years little change was noted during the last eight years. Two patients experienced improvement after PTX but six did not. Two patients (SIA and SJ) showed a blunted photon absorption profile of the radius bones (Fig. 7).

Bone biopsies of the iliac crest were taken 12 times in 8 patients (Table 2). The osteoclast activity was remarkably high in all patients but two (EG and IJ) and in all patients as a group when compared to normal and to other RDT-patients. All patients with high osteoclast activity were later parathyroidectomized although the biopsy results were not available before operation. A decrease in the osteoclast count was noted in one patient (IO) before PTX was performed. The osteoid surface was increased in three patients. The course in one of the patients followed for 16 years is shown in Fig. 8.

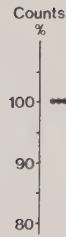


Figure 7. An example of a blunted photon absorption profile of os radius in densitometry (patient SJ).

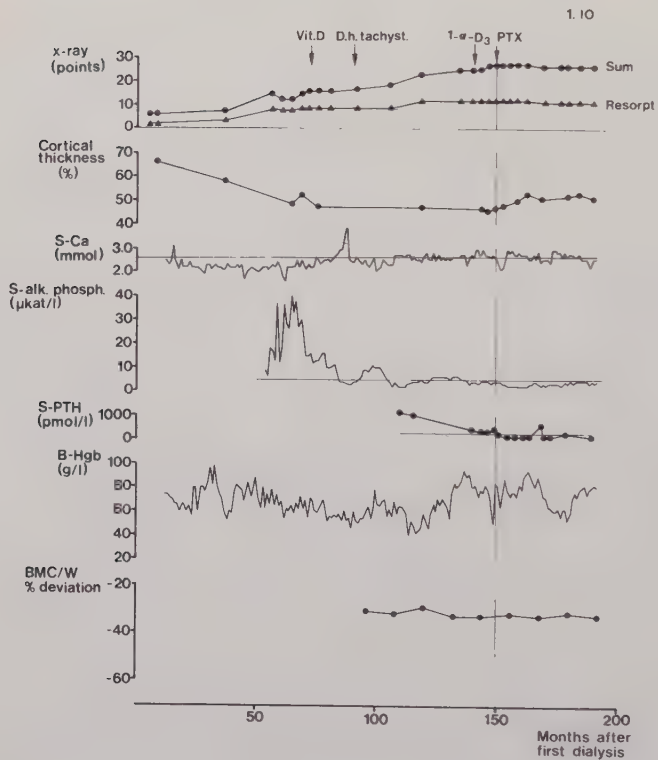


Figure 8. Some characteristics in X-ray, laboratory tests and densitometry in one patient (IO) followed for 16 years on RDT.

Discussion

The material of patients dialyzed for 10 years or more is small. On the other hand it includes two patients who have now been dialyzed for more than 16 years. Already in 1975 they belonged to the group of four who according to the EDTA registry (14) were dialyzed for the largest number of years. Both these patients married after about 10 years in dialysis and besides taking care of the home they are working part time. One of the patients (I0) is in excellent condition, the other patient (SJ) has intermittently vascular access problems.

Both these patients and three of the others showed a steady increase in the skeletal changes on X-ray. However, it was also noted that all patients had at least some abnormality already at the start on RDT, mostly as decalcification, but also resorption and metastatic calcification were found. Bone densitometry was not available when these patients were started but we have recently shown that most of the mineral loss noted in RDT patients followed for up to 2 years, started in 1973 or later, was due to loss before the start of active uremia treatment (to be published). In this material very little further abnormalities have appeared during the last years and then mostly metastatic calcification. The most dramatic changes were noticed after PTX. Three patients (K0, ELH and SA) were parathyroid-ectomized relatively early in their dialysis course (Table 3), and they showed clear improvements in bone resorption, laboratory values and two also in bone mineral content.

However, in four patients operated later (I0, SJ, SIA and ML) very little improvement could be seen (Table 3). One patient (BP) who was parathyroid-ectomized after 85 months on RDT without improvement also suffered from rheumatoid arthritis and took antiepileptic drugs for the last 11 years. Parathyroidectomy thus seems to have little effect when done late in the dialysis course. Since also the S-PTH before PTX was relatively low in these patients, and one of them (I0, Table 2), in whom repeat bone biopsies were performed, showed a continuous decrease in osteoclast activity, it seems possible that the parathyroid glands were burnt out. Spontaneous regression seems, however, to be possible early in dialysis as seen on X-ray examination in one patient (IJ, Fig. 2).

In bone densitometry an unusual, blunted absorption profile of the radius bone was seen in two patients (SIA and SJ) instead of the double peaked curve caused by a tubular bone (Fig. 7). This probably signifies a severe loss of intra-cortical bone (15). The cortical thickness measured on the

Table 2. Results of iliac crest bone biopsy in patients followed for ≥ 10 years in RDT

Patient	Months after start on RDT	Osteoclast activity (number/mm ²)	Osteoid surface (%)	Parathyroidectomy (months after start)
1. IO	83	0.94	0.2	150
	106	0.58	8.1	-
	135	0.31	5.0	-
2. SJ	86	0.48	1.3	163
	142	0.72	31.5	-
4. SIA	36	0.79	23.2	91
5. EG	31	0.13	10.0	-
	52	0.34	9.6	-
6. ML	58	1.17	11.9	104
8. ELH	15	0.76	16.7	43
9. SA	15	0.75	5.7	41
10. IJ	12	0.36	11.5	-
Normal subjects, mean $\pm$ 1 SD, N = 86		0,03 $\pm$ 0.02	2,4 $\pm$ 3,5	
Other patients on RDT, mean $\pm$ 1 SD, N = 72		0,32 $\pm$ 0.26	15 $\pm$ 16	

metacarpal bones is also a parameter of bone mass and it showed low values in the same patients (Fig. 5). One patient (SJ) did worse than one other (IO) in spite of almost identical age, sex and treatment. The only difference was that the first was taking antiepileptic drugs for the last 10 years.

The potent 1- α -D₃ vitamin was used during the last four years in five patients. Besides decrease in alkaline phosphatase in three and in S-PTH in one, no effect on X-ray or bone densitometry findings could be seen. However, an increase in metastatic calcifications were noticed in three patients and perhaps this is the prize which has to be paid in order to prevent progression in the bone changes. Aluminium content in the water for dialysis fluid preparation was only measured during the last year but is probably a poor parameter of Al-intoxication, and no correlations to the skeletal changes could be seen.

Table 3. Results of Parathyroidectomy (PTX)

Patient	PTX (mths after start)	Radiological			Densitometry	Laboratory			
		Erosions	Calcifications	Cortical thickness	Bone mineral content	S-Ca	Alk phosph	PTH	Hgb
1. IO	150	↓	↑	↑	-	↓↓	-	↓	↑
2. SJ	163	-	↑	-	-	↓↓	=	-	↑
3. BP	85	-	-	↓	↓	-	↓↓	-	↓
4. SIA	91	↑	↑	↓	-	↓↓	↓↓	↓	↑
6. ML	104	↓	-	↑	-	-	↓↓	-	-
7. KO	87	↓↓	-	↓	-	↓↓	↓↓	↓↓	-
8. ELH	43	↓↓	-	↑	↑↑	↓	↓	↓↓	↓
9. SA	41	↓↓	↓	-	↑↑	↓↓	↓↓	↓	-

↑↑ or ↓↓ denotes clear change, ↑ or ↓ probable change, - no change.

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"Let us celebrate this happy meeting (with the stone) with a convivial glass". (Dickens 1836).



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